CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

19-386

Administrative/Correspondence

Department of Health and Human Services
Public Health Service
Food and Drug Administration

Memorandum

Date: DEC 29 1986

To: Director
Office of Drug Research and Review, HFN-100

Through: Director
Division of Cardio-Renal Drug Products, HFN-110

From: Ronald Lieberman, M.D., Medical Officer
Division of Cardio-Renal Drug Products, HFN-110

Subject: NDA 19-386 Esmolol
First Safety Update Volumes 5.1 and 5.2
July 22, 1985

Per our meeting today in your office the following information is provided. In essence, the medical officer's review (MOR) completed March 11, 1986 reflects and incorporates the information contained in the safety update cited above. This report contains safety data on the 120 patients and normal subjects who received Brevibloc in ongoing clinical studies during the period from September 30, 1984 (the "date lock point" for the original NDA) to April 18, 1985 (the "date lock point" for this report). It also contains case reports for the thirteen (13) patients in whom administration of the study drug was discontinued due to an ADE. It also contains data for the two CABG studies (8052-83-27 and 8052-83-56).

For further details re safety and ADE, please refer to the MOR March 11, 1986.

Ronald Lieberman, M.D.

cc
~~Orig.~~
HFN-110
~~HFN-110/CSO~~
HFN-110/RLieberman;12/29/86
sb/12/29/86;12/29/86/4715s

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Division Director's Review

NDA: 19-386

Sponsor: Dupont Critical Care
Waukegan, IL

Name of Drug: Esmolol

Resume: This is the third safety update since the original submission of this NDA. The review package is currently with the office under consideration for approval.

This safety update contains all information up to December 2, 1986, and is cumulative , i.e., contains all information including that previously reported. It covers data from 432 patients and 82 normal subjects. It also contains case report forms for 27 patients in whom administration of study drug was discontinued due to an adverse experience (minus) which were previously submitted; so 20 case report forms are in this submission.

There is essentially no change in the spectrum of adverse effects in this submission when compared to those already documented and already a part of proposed labelling.

RL 12/18/86

Raymond J. Lipicky, M.D.

cc: Orig. NDA
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HFN-110/CSO
HFN-110/RLipicky:12/16/86
ef:12/17/86:4073Pq

Department of Health and Human Services
Public Health Service
Food and Drug Administration

Memorandum

Date:

To: Director
Office of Drug Research and Review, HFN-100

From: Director
Division of Cardio-Renal Drug Products, HFN-110

Subject: Review of Safety Update for NDA 19-386 Previblоc (esmolol) Injection

With exception of trials in progress regarding dose finding for [redacted] we have received all of the adverse drug reaction data from all trials. These adverse reactions are addressed in the labeling. Therefore, no further safety update is needed at this time.

Raymond J. Lipicky, M.D.

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Orig.
HFN-110
~~HFN-110/CSO~~
HFN-110/NMorgenstern/12/1/86;12/1/86
sb/12/1/86;12/1/86/4582s

Department of Health and Human Services
Public Health Service
Food and Drug Administration

Memorandum

DATE: NOV 2 4 1986

FROM: Director
Division of Cardio-Renal Drug Products, HFN-110

SUBJECT: NDA 19-386, Esmolol, Dupont Critical Care

TO: Director
Office of Drug Research and Review, HFN-100

This is the second transmittal memorandum regarding NDA 19-386. The first one, dated July 28, 1986, still is a reasonable summary of my thoughts. However, since that memo, three things have happened:

a) There was a meeting of the Cardio-Renal Advisory Committee.

b) As a result of that meeting, the Division has changed its opinion regarding approvability of esmolol. The Committee and the Division recommend approval of esmolol for short-term control of ventricular rate in patients with atrial flutter/fibrillation. The Committee was rather decisive regarding the perioperative indication. The Committee's thinking with regard to both indication, at least as I interpreted it, is summarized below.

c) American Critical Care was merged with Dupont, and is now known as Dupont Critical Care.

Control of Ventricular Rate

The Committee was not comfortable with the effects of esmolol on blood pressure. In spite of adequate basic animal pharmacology, there was no decisive judgment that the hemodynamic effects of esmolol were simply due to its cardioselective beta blockade. Indeed, the Committee desired more head-to-head comparisons of brevibloc to metoprolol and atenolol in patients. In spite of the inability to feel totally comfortable with the blood pressure effects of esmolol, the Committee did not believe that the blood pressure effects were of sufficient concern to preclude use in a patient population where short-term control of ventricular rate was an appropriate therapeutic goal. Such patient populations exist; for example, those patients who have had surgical valve repair or prosthetic valve placement and experience transient atrial flutter/fibrillation that occurs postoperatively. In these circumstances, the arrhythmia is transient (one or two days) and control of ventricular rate with an easily titrated drug is clinically indicated.

In other circumstances, i.e., chronic atrial flutter/fibrillation, where either conversion or long-term control of ventricular rate is needed, two factors weigh risks higher than benefits.

a) Since esmolol's effects regress rapidly upon termination of infusion (the effects are gone in 10 or 20 minutes), another drug (i.e., digoxin, verapamil or some long-acting beta blocker) would need to be started for maintenance. Thus, titration with two drugs (first esmolol, then other drugs) would invariably be necessary. Two dose-related adverse effect risks would be necessary.

b) Blood pressure lowering effects of esmolol, to achieve only short-term control, were thought to be unacceptable when esmolol alone was not the final therapy.

The Division concurs with the overall judgment. A suitably revised package insert is appended.

Raymond J. Lipicky, M.D.

Attachment

cc: Orig. NDA
HFN-110
HFN-110/CSO
HFN-110/PLipicky:10/10/86;10/28/86
R/D:ef:10/14/86;sb/10/28/86;10/29/86;10/31/86:#0651g
R/D: CHenry/10/29/86
NMorgenstern/10/29/86

October 23, 1986

Minutes of Meeting
Between
DuPont Critical Care
and
Food and Drug Administration

DuPont Critical Care Participants
Kenneth G. Kasses, Ph.D President
Robert J. Lee, Ph.D Vice President Research and Development, Surgical/Critical Care Group, Travenol Laboratories Inc

Food and Drug Administration Participants
Raymond Lipicky, M.D., Director, Division of Cardio-Renal Drug Products.
Ronald Liberman, M.D. Medical Officer
Constance Burner Henry, Consumer Safety Officer

Subject: Esmolol NDA 19386

This meeting was held with DuPont Critical Care to discus the approvability of their drug product Esmolol (Brevibloc).

Dr. Lipicky felt that there was not much to discuss after the recent advisory committee meeting. We will send the NDA for supraventricular tachycardia to Dr.Temple.

The meeting was adjourned.

Constance Burner Henry
Consumer Safety Officer

cc:
Orig NDA 19-386
HFN-110
HFN-110/SBenton
HFN-110/CHenry
0826r

Department of Health and Human Services
Public Health Service
Food and Drug Administration

Memorandum

Date: July 28, 1986

To: Director
Office of Drug Research and Review, HFN-100

From: Director
Division of Cardio-Renal Drug Products, HFN-110

Subject: Non-approval of NDA 19-366, Esmolol, American Critical Care

American Critical Care has submitted clinical trials in support of two claims:

a) Control of ventricular response in the face of supraventricular tachycardias.

This NDA has been a particularly difficult decision making exercise and I am still not comfortable with the position the Division has elected. Consequently, I have scheduled esmolol to be presented to the Cardio-Renal Advisory Committee at its next meeting (September 28 and 29, 1986). The Anesthesia Advisory Committee will be suitably represented at this meeting. If they disagree with the Division's position, I am willing to reverse my decision. Nevertheless, I have evolved a position, am prepared to act, and consequently the attached materials constitute the Division's recommendation that the application be not approved. In the case of control of ventricular response, esmolol has unacceptable risks that outweigh its benefit.

The clinical trials conducted by the sponsor, the indications sought and the general strategy with respect to how to achieve approval were the subject of meetings between American Critical Care and the Division. We were all in concordance on each point. The trials that were conceived were appropriate, were conducted well and data analysis and reporting have been exemplary. The Division, the medical community, practicing anesthesiologists and you (as the Office Director) all think a rapidly acting beta blocker would be a welcome armamentarium if one were available in the marketplace. Yet, the results of the trials that were to "win approval" contradict all of our preconceived biases, or perhaps, the indications sought were just a poor choice and another pursuit would have been more fruitful.

The Summary Basis of Approval was written by American Critical Care with my direction. The data are accurately represented. Conclusions and arguments for approval are American Critical Care's, left intact. This was a purposeful happening. Since this is a close judgement call I thought you should see the best argument that could be constructed from the data. Data presentation in the document is not misleading.

My interpretive comments follow.

Control of Ventricular Response

All six trials shared the same mode of administration of esmolol, namely, infusion at constantly increasing doses until a maximum dose of 200 micrograms/kg/min was achieved. One trial (8052-81-05) was placebo controlled, one trial (8052-81-04) was positively controlled with propranolol, the remainder were simply baseline controlled.

There is no question, the use of esmolol increased the functional A-V refractory period which resulted in a decrease in ventricular rate, without an alteration in the atrial arrhythmia (there are occasional exceptions in patients with paroxysmal atrial tachycardia). The sponsor, rightfully so, makes no claim with respect to altering the atrial arrhythmia or conversion to normal sinus rythm. In the 8052-81-04 trial, propranolol and esmolol were indistinguishable with respect to their abilities to control ventricular rate.

In the trials, oriented toward getting to the maximal planned dose of esmolol, there was considerable hypotension due to esmolol. The definition of hypotension is set forth by American Critical Care in the SbA and its incidence was between 20 and 25% across the studies. In study 8052-81-04, the propranolol positive control study, esmolol's use was associated with hypotension in 23 out of 64 patients (34%) and 25% of patients were terminated from the study because of hypotension. In the same study propranolol's use was associated with hypotension in only 4 out of 64 patients (6%) and none were terminated because of hypotension. Control of ventricular response was not distinguishable between esmolol and propranolol.

In studies 8052-82-05, 8052-83-20 and 8052-83-30 there was about a 50% of total adverse drug reactions attributable to esmolol and terminations due to an adverse reaction ranged between 20 and 25%.

True that all these "bad" things reverse quickly and true that in practice one might stop at lower rates of infusion, however, why in the world does the safety margin appear so narrow. Propranolol, a beta blocker, controlled ventricular response adequately without a prominent hypotensive effect. Why does the beta blocker esmolol have such a prominent hypotensive effect?

Such questions are not addressed by data within the NDA. I know of no experiments designed to answer the questions. On the face of it, I can easily postulate that esmolol has some effect other than beta blockade which leads to more hypotension than expected. It seems to me that until that postulate is refuted, we should consider esmolol incompletely characterized and that the transient control of ventricular response (i.e., only there while esmolol is being infused intravenously) is just not worth the risk. Consequently, the indication cannot be approved.

So in balance, I cannot find a good, data dependent, argument to support approval. Being a physician, I like all the physicians I have talked to would like to see esmolol approved. Nonetheless, lacking data dependent arguments, I must recommend non-approval.

I look forward to your insights and to the insights of the Advisory Committee.

Raymond J. Lipicky, M.D.

cc
Orig.
HFN-110
HFN-110/CSO
HFN-110/RLipicky/7/26/86
sb/7/26/86:7/28/86:3964s

M E M O R A N D U M

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drugs and Biologics
Office of Drug Standards

DATE : JUN 9 1986

TO : Jerome P. Skelly, Ph.D.
Director,
Division of Biopharmaceutics
HFN-220

FROM : CT Viswanathan, Ph.D.
Acting Chief,
Pharmacokinetics Evaluation Branch
HFN-226

SUBJECT: Esmolol HCl (Brevibloc)
NDA 19-386

Supervisory Comment:

Pharmacokinetic Data from Hepatic and Renal Disease Patients:

In light of the conversation between the reviewer and the sponsor, it is learned that studies on these patient subgroups have been completed. Furthermore, it is understood from the item #2 under overall conclusion that "the elimination half-life (acid metabolite) in these patients was increased about ten times that in normals and plasma levels were considerably elevated". *Therefore it is necessary* that this data be submitted for evaluation by the Agency and the labeling be updated for dose adjustment in these patients. A clinical judgement needs to be made as to the importance of the "indicated" tenfold increase of acid metabolite and increased elimination half life.

CT. Viswanathan

CT Viswanathan, Ph.D.

Appendix A

- Dose Proportionality

Table 1

Concentrations of Brevibloc (ng/mL) and its Metabolite (mcg/mL) in Blood

Mean ± Standard Deviation (n)

Time, minutes	Dose: mcg/kg/min - 6 Hour Infusion							
	50		100		200		300	
	Brevibloc	Metabolite	Brevibloc	Metabolite	Brevibloc	Metabolite	Brevibloc	Metabolite
15	111 ± 14 (4)	BQL (6)	290 ± 135 (5)	BQL (6)	546 ± 327 (6)	BQL (6)	1070 ± 510 (7)	1.43 ± 0.94 (8)
30	150 ± 46 (4)	BQL (7)	278 ± 166 (8)	1.46 ± 0.73 (6)	615 ± 292 (6)	3.65 ± 1.00 (6)	999 ± 739 (7)	6.86 ± 2.18 (7)
60	170 ± 73 (4)	2.17 ± 0.87 (7)	328 ± 208 (8)	5.00 ± 0.95 (8)	575 ± 207 (6)	10.1 ± 1.8 (8)	1270 ± 300 (7)	20.8 ± 5.4 (8)
120	140 ± 58 (3)	6.23 ± 1.25 (8)	298 ± 163 (8)	12.5 ± 1.3 (7)	933 ± 455 (6)	24.1 ± 3.2 (8)	986 ± 436 (7)	47.0 ± 12.5 (8)
180	196 ± 49 (3)	9.70 ± 2.29 (7)	334 ± 196 (8)	18.7 ± 2.6 (7)	694 ± 200 (6)	38.4 ± 3.6 (8)	1210 ± 600 (7)	71.0 ± 16.3 (8)
240	192 ± 65 (3)	12.8 ± 2.8 (8)	335 ± 187 (8)	24.5 ± 2.8 (8)	605 ± 487 (5)	49.1 ± 7.2 (8)	841 ± 194 (7)	93.0 ± 20.0 (8)
300	152 ± 31 (4)	14.8 ± 3.0 (8)	273 ± 196 (8)	28.8 ± 3.4 (8)	869 ± 458 (5)	55.5 ± 7.0 (8)	866 ± 409 (7)	116 ± 28 (8)
360	116 ± 24 (4)	17.1 ± 2.9 (8)	305 ± 198 (8)	32.1 ± 4.7 (8)	637 ± 237 (6)	62.4 ± 7.8 (8)	792 ± 462 (7)	130 ± 25 (7)
361	125 ± 38 (4)	17.2 ± 2.8 (8)	254 ± 114 (8)	32.3 ± 4.2 (8)	653 ± 238 (6)	65.2 ± 12.2 (8)	719 ± 151 (7)	129 ± 26 (7)
362	98.7 ± 10.8 (4)	17.7 ± 3.2 (8)	187 ± 68 (8)	32.8 ± 3.5 (8)	444 ± 133 (5)	64.2 ± 9.9 (8)	621 ± 247 (7)	123 ± 27 (8)
364	66.2 ± 9.7 (4)	17.7 ± 3.1 (8)	120 ± 42 (8)	32.6 ± 4.5 (8)	262 ± 89 (6)	65.0 ± 10.1 (8)	413 ± 150 (6)	127 ± 27 (8)
366	41.1 ± 21.1 (4)	16.9 ± 3.6 (7)	84.1 ± 37.4 (8)	32.9 ± 4.1 (8)	209 ± 65 (5)	64.1 ± 6.2 (8)	286 ± 96 (7)	125 ± 31 (8)
368	31.9 ± 16.7 (4)	17.7 ± 3.0 (7)	63.1 ± 32.7 (8)	32.6 ± 4.7 (8)	141 ± 92 (6)	65.6 ± 6.8 (8)	204 ± 80 (7)	125 ± 25 (8)
370	29.4 ± 22.5 (4)	17.7 ± 4.0 (7)	49.8 ± 26.1 (8)	32.8 ± 4.5 (8)	112 ± 102 (6)	65.8 ± 9.1 (8)	172 ± 80 (7)	127 ± 31 (8)
372	24.3 ± 15.9 (4)	17.3 ± 3.3 (7)	39.2 ± 20.0 (8)	33.0 ± 3.8 (8)	88.3 ± 96.4 (6)	65.4 ± 8.1 (7)	145 ± 93 (5)	126 ± 29 (8)

NR - Data are not retrievable.

BQL - Below quantitation limits of 23.1 ng/mL for Brevibloc or 0.925 mcg/mL for the metabolite, ASL-8123.

seems to be suggestive of dose-independent disposi

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Table I (continued)

Concentrations of Brevibloc (ng/mL) and its Metabolite (mcg/mL) in Blood

Mean ± Standard Deviation (n)

Time, minutes	Dose: mcg/kg/min - 6 Hour Infusion							
	50		100		200		300	
	Brevibloc	Metabolite	Brevibloc	Metabolite	Brevibloc	Metabolite	Brevibloc	Metabolite
374	BQL (4)	17.4 ± 3.7 (7)	33.5 ± 14.4 (6)	33.0 ± 3.9 (8)	66.5 ± 82.0 (6)	63.6 ± 7.4 (8)	95.6 ± 63.9 (6)	126 ± 28 (8)
376	BQL (4)	16.3 ± 3.4 (6)	39.4 ± 21.5 (7)	32.8 ± 4.6 (8)	89.1 ± 97.5 (6)	64.4 ± 5.4 (8)	83.0 ± 42.6 (6)	126 ± 27 (8)
378	BQL (4)	17.2 ± 3.1 (8)	26.7 ± 14.2 (7)	33.6 ± 4.7 (8)	64.6 ± 80.6 (6)	63.7 ± 7.3 (8)	73.5 ± 35.1 (7)	125 ± 29 (8)
381	BQL (4)	17.3 ± 2.8 (8)	BQL (6)	33.3 ± 4.2 (8)	66.2 ± 73.9 (5)	64.8 ± 5.2 (8)	56.0 ± 30.1 (5)	124 ± 28 (8)
384	BQL (4)	16.5 ± 2.3 (8)	BQL (7)	33.8 ± 4.3 (8)	25.3 ± 19.4 (6)	63.4 ± 5.8 (8)	37.2 ± 24.3 (7)	128 ± 29 (8)
390	BQL (4)	17.0 ± 3.0 (8)	BQL (8)	32.3 ± 3.9 (8)	BQL (6)	64.3 ± 7.9 (8)	BQL (7)	125 ± 30 (8)
396	BQL (4)	16.9 ± 2.7 (8)	BQL (8)	32.3 ± 4.3 (8)	BQL (5)	63.1 ± 6.4 (8)	BQL (6)	120 ± 22 (8)
420	BQL (4)	15.3 ± 2.7 (7)	BQL (8)	31.1 ± 3.7 (8)	BQL (6)	59.7 ± 6.5 (8)	BQL (7)	121 ± 24 (8)
480	BQL (4)	13.6 ± 1.7 (8)	BQL (8)	26.8 ± 3.7 (8)	BQL (5)	51.2 ± 5.5 (8)	BQL (7)	99.6 ± 22.2 (8)
600	BQL (4)	8.96 ± 1.77 (7)	BQL (7)	17.8 ± 2.5 (8)	BQL (2)	36.4 ± 5.8 (8)	BQL (5)	69.6 ± 19.3 (7)
720	BQL (4)	6.28 ± 0.96 (6)	BQL (6)	12.1 ± 1.8 (8)	BQL (2)	25.2 ± 5.4 (8)	BQL (5)	47.2 ± 12.7 (7)
840	BQL (4)	4.28 ± 2.27 (5)	BQL (6)	8.07 ± 1.55 (8)	BQL (2)	16.8 ± 4.4 (8)	BQL (5)	32.2 ± 9.2 (7)
960	BQL (4)	2.21 ± 1.22 (4)	BQL (5)	5.47 ± 1.39 (7)	BQL (2)	12.5 ± 3.4 (7)	BQL (4)	22.4 ± 7.5 (6)
1200	BQL (4)	BQL (4)	BQL (6)	2.68 ± 1.48 (5)	BQL (2)	6.64 ± 2.10 (7)	BQL (4)	12.7 ± 5.1 (7)
1440	BQL (3)	BQL (3)	BQL (2)	1.24 ± 0.47 (5)	BQL (2)	3.16 ± 1.85 (6)	BQL (5)	7.00 ± 2.87 (7)

BQL - Below quantitation limits of 23.1 ng/mL for Brevibloc or 0.925 mcg/mL for the metabolite, ASL-8123.

Table 2

Concentrations of Brevibloc (ng/mL) and its Metabolite (mcg/mL) in Blood

Mean ± Standard Deviation (n)

150 mcg/kg/min - 24 Hour Infusion

Time, min	Brevibloc	Metabolite
15	364 ± 142 (8)	BQL (6)
30	509 ± 216 (8)	3.11 ± 0.85 (7)
60	523 ± 132 (7)	8.15 ± 1.68 (7)
120	533 ± 252 (8)	19.9 ± 3.6 (8)
180	611 ± 399 (8)	28.3 ± 5.7 (8)
240	532 ± 329 (8)	38.2 ± 4.2 (8)
360	522 ± 190 (6)	55.0 ± 3.6 (7)
720	443 ± 142 (6)	63.9 ± 11.3 (7)
1080	295 ± 72 (8)	69.9 ± 10.6 (7)
1440	338 ± 177 (7)	64.6 ± 9.6 (8)
1441	441 ± 377 (7)	63.0 ± 7.6 (8)
1442	356 ± 200 (7)	65.4 ± 9.2 (8)
1444	194 ± 93 (8)	63.4 ± 11.2 (8)
1446	129 ± 61 (8)	63.5 ± 10.3 (8)
1448	109 ± 50 (8)	64.9 ± 11.4 (8)
1450	88.5 ± 43.4 (8)	63.7 ± 11.1 (8)
1452	69.6 ± 24.4 (8)	66.3 ± 10.0 (8)
1454	59.8 ± 23.6 (8)	64.8 ± 10.1 (8)
1456	57.7 ± 27.3 (8)	65.3 ± 9.2 (8)
1458	56.5 ± 31.4 (7)	64.2 ± 7.5 (8)
1461	38.6 ± 31.6 (8)	64.3 ± 7.7 (8)
1464	33.7 ± 26.3 (8)	64.6 ± 7.7 (8)
1470	26.6 ± 23.6 (8)	64.0 ± 6.4 (8)
1476	BQL (8)	63.0 ± 7.1 (8)
1500	BQL (8)	62.9 ± 8.3 (8)
1560	BQL (8)	53.0 ± 7.3 (8)
1680	BQL (8)	37.6 ± 6.9 (8)
1800	BQL (8)	29.5 ± 5.3 (7)
1920	BQL (8)	21.7 ± 3.9 (7)
2040	BQL (8)	16.2 ± 3.0 (8)
2280	BQL (8)	8.08 ± 1.88 (8)
2520	BQL (8)	4.70 ± 1.06 (8)

BQL - Below quantitation limits of 23.1 ng/mL for Brevibloc or 0.025 mcg/mL for the metabolite, ASL-8123.

Table 3

Plasma Level of Methanol (mcg/mL) and Formate (mcg/mL)

Subject		Dose, mcg/kg/min (measurement time)						
		50 (6 hr)	100 (6 hr)	200 (6 hr)	300 (6 hr)	150 (6 hr)	150 (12 hr)	150 (24 hr)
1	methanol	*	*	5.07	3.05	*	3.08	2.85
	formate	*	*	*	2.68	*	*	*
2	methanol	*	*	2.11	4.15	*	3.56	13.15
	formate	*	*	4.03	*	*	*	*
3	methanol	9.52	*	3.90	5.89	*	3.44	5.21
	formate	*	3.90	4.19	*	*	*	*
4	methanol	*	2.03	3.71	3.89	3.17	3.64	2.84
	formate	*	*	*	*	4.19	2.91	4.33
5	methanol	2.27	*	3.26	4.77	2.95	3.28	2.88
	formate	*	NS	*	*	*	*	*
6	methanol	*	*	4.39	2.77	2.64	2.98	4.94
	formate	*	*	*	2.50	*	2.68	*
7	methanol	*	*	2.58	4.34	2.32	2.74	4.24
	formate	*	*	*	*	*	*	*
8	methanol	2.62	*	2.35	3.28	2.58	2.98	3.40
	formate	*	NS	*	*	*	2.80	2.62
mean of methanol ± S.D.		--	--	3.42 1.04	4.02 1.02	--	3.21 0.32	4.94 3.45

* Levels were below the detection levels of the assays (2.0 mcg/mL for methanol and 2.5 mcg/mL for formate).

NS - No sample.

levels look good

Table 4

Summary of Excretion of Brevibloc and ASL-8123 by Dosage

Dosage	Brevibloc Mean Excretion (mg)	Brevibloc % Dose Excretion	ASL-8123 Mean Excretion (mg)	ASL-8123 % Dose Excretion*
50	8.63 ± 4.17	0.647 ± 0.313	929 ± 142	73.0 ± 2.52
100	18.0 ± 6.10	0.672 ± 0.182	1850 ± 405	72.5 ± 9.33
200	42.5 ± 18.9	0.779 ± 0.288	3740 ± 508	73.9 ± 4.62
300	76.6 ± 23.5	~~0.988~~ ± 0.361	5860 ± 1230	77.7 ± 9.43
150	113 ± 51.0	0.694 ± 0.239	10500 ± 2100	69.2 ± 9.91

* ASL-8123 excretion calculated as $\frac{\text{(amount excreted)(1.05)}}{\text{Total Dose Infused}}$ OK

Table 5

Steady-State Blood Levels of Brevibloc, ng/mL

	Dose (mcg/kg/min)				
Subject	50	100	150	200	300
1					
2					
3					
4					
5					
6					
7					
8					
Mean	156	312	479	711	993
± S.D.	32	145	195	277	280
n	4	8	8	6	7

All concentrations measured between 1 hour after start of infusion and the end of infusion were used to calculate the mean steady-state concentration by subject and by dose.

* Without Subject #5, the mean ± S.D. = 603 ± 92 (5).

NR - not retrievable.

Table 6

Terminal Half-Life of Brevibloc, hours

Subject	Dose of Brevibloc (mcg/kg/min) 50	100	150	200	300	Mean ± S.D. (n)
1						0.135 ± 0.066 (4)
2						0.115 ± 0.100 (3)
3						0.159 ± 0.096 (4)
4						0.109 ± 0.014 (4)
5						0.130 ± 0.030 (4)
6						0.140 ± 0.065 (4)
7						0.116 ± 0.051 (5)
8						~~0.166 (2)~~
Mean	0.130	0.120	0.174	0.139	0.0985	
± S.D.	0.072	0.048	0.067	0.064	0.276	
n	4	8	7	4	7	

Overall Mean ± S.D. (n): 0.131 ± 0.058 (30) hours or 7.88 ± 3.48 minutes.

NR - not retrievable.

Table 8

Total Body Clearance of Brevibloc, L/kg/hour

	Dose of Brevibloc (mcg/kg/min)					
Subject	50	100	150	200	300	Mean ± S.D. (n)
1						14.8 ± 3.9 (4)
2						30.5 ± 9.2 (4)
3						24.7 ± 13.6 (4)
4						15.9 ± 5.3 (4)
5						20.9 ± 8.4 (4)
6						17.6 ± 3.9 (4)
7						19.3 ± 1.5 (5)
8						23.9 ± 4.8 (4)
Mean	19.9	24.1	21.3	18.5	19.4	
± S.D.	4.1	12.8	7.6	5.2	5.4	
n	4	8	8	6	7	

Overall Mean ± S.D. (n): 20.9 ± 8.0 (33).

NR - not retrievable.

Table 7

Steady-State Volume of Distribution of Brevibloc, L/kg

	Dose of Brevibloc (mcg/kg/min)					
Subject	50	100	150	200	300	Mean ± S.D. (n)
1						1.81 ± 0.90 (4)
2						3.80 ± 2.29 (3)
3						3.11 ± 1.67 (4)
4						1.36 ± 0.56 (4)
5						2.76 ± 1.35 (4)
6						2.02 ± 0.76 (4)
7						1.77 ± 0.62 (5)
8						4.02 (2)
Mean	2.63	2.47	3.13	1.58	2.01	
± S.D.	1.44	1.54	1.49	0.76	1.14	
n	4	8	7	4	7	

Overall Mean ± S.D. (n): 2.42 ± 1.36 (30).

NR - not retrievable.

* For calculation of AUC, estimated 1440 min sample concentration as 331 ng/mL, the steady-state concentration.

Table 9

Predicted Steady-State Concentrations of ASL-8123, mcg/mL

	Dose of Brevibloc (mcg/kg/min)				
Subject	50	100	150	200	300
1					
2					
3					
4					
5					
6					
7					
8					
Mean	25.3	51.3	74.6	103	202
± S.D.	5.1	7.6	9.2	16	50
n	7	8	8	8	7

NR - not retrievable.

Table 10

Terminal Half-Life of ASL-8123, hours

	Dose of Brevibloc (mcg/kg/min)					
Subject	50	100	150	200	300	Mean ± S.D. (n)
1						4.57 ± 0.35 (5)
2						3.86 ± 0.29 (5)
3						3.93 ± 0.59 (5)
4						4.13 ± 0.43 (5)
5						3.64 ± 1.01 (5)
6						3.88 ± 0.43 (5)
7						4.29 ± 0.35 (4)
8						4.02 ± 0.38 (4)
Mean	3.57	3.85	4.62	3.93	4.16	
± S.D.	0.72	0.31	0.27	0.51	0.33	
n	7	8	8	8	7	

Overall Mean ± S.D. (n): 4.03 ± 0.56 (38).

NR - not retrievable.

Table 11

Total Body Clearance of ASL-8123, L/kg/hr

	Dose of Brevibloc (mcg/kg/min)					
Subject	50	100	150	200	300	Mean ± S.D. (n)
1						0.0615 ± 0.0118 (5)
2						0.0923 ± 0.0162 (5)
3						0.0839 ± 0.0207 (5)
4						0.0868 ± 0.0070 (5)
5						0.0910 ± 0.0165 (5)
6						0.0848 ± 0.0178 (5)
7						0.0887 ± 0.0073 (4)
8						0.0900 ± 0.0046 (4)
Mean	0.0903	0.0859	0.0845	0.0878	0.0740	
± S.D.	0.0173	0.0151	0.0151	0.0134	0.0188	
n	7	8	8	8	7	

Overall Mean ± S.D. (n): 0.0846 ± 0.0160 (38).

NR - not retrievable.

Table 12

Volume of Distribution of ASL-8123, L/kg

	Dose of Brevibloc (mcg/kg/min)					
Subject	50	100	150	200	300	Mean ± S.D. (n)
1						0.402 ± 0.063 (5)
2						0.512 ± 0.096 (5)
3						0.470 ± 0.097 (5)
4						0.518 ± 0.073 (5)
5						0.460 ± 0.084 (5)
6						0.468 ± 0.076 (5)
7						0.550 ± 0.081 (4)
8						0.522 ± 0.070 (4)
Mean	0.455	0.472	0.560	0.482	0.438	
± S.D.	0.086	0.047	0.088	0.064	0.099	
n	7	8	8	8	7	

Overall Mean ± S.D. (n): 0.485 ± 0.085 (38).

NR - not retrievable.

Table 19

Pharmacokinetic Summary

Parameter Mean ± Standard Deviation (n)

Brevibloc

	Dose of Brevibloc (mcg/kg/min)																	
Parameter	50			100			150			200			300			Overall		
C_{ss}, ng/mL	196	± 32	(4)	312	± 149	(8)	479	± 195	(8)	605	± 92	(5)	993	± 279	(7)	---		
$T_{1/2}$, hours	0.130	± 0.072	(4)	0.120	± 0.048	(4)	0.174	± 0.067	(7)	0.139	± 0.064	(4)	0.0985	± 0.0276	(7)	0.131	± 0.058	(30)
Cl, L/hr/kg	19.9	± 4.1	(4)	24.1	± 12.8	(8)	21.3	± 7.6	(8)	18.9	± 5.2	(6)	19.4	± 5.4	(7)	20.9	± 8.0	(33)
V_{ss}, L/kg	2.83	± 1.44	(4)	2.47	± 1.94	(8)	3.13	± 1.49	(7)	1.38	± 0.76	(4)	2.01	± 1.14	(7)	2.42	± 1.36	(30)

ASL-8123

	Dose of Brevibloc (mcg/kg/min)																	
Parameter	50			100			150			200			300			Overall		
$C_{ss,av}$, mcg/mL (predicted)	25.3	± 5.1	(7)	51.3	± 7.6	(8)	74.6	± 9.2	(8)	103	± 16	(8)	202	± 50	(7)	---		
$T_{1/2}$, hours	3.57	± 0.72	(7)	3.89	± 0.31	(8)	4.62	± 0.27	(8)	3.95	± 0.51	(8)	4.16	± 0.33	(7)	4.03	± 0.56	(53)
Cl_{ss}, L/hr/kg	0.0903	± 0.0173	(7)	0.0859	± 0.0151	(8)	0.0845	± 0.0151	(8)	0.0878	± 0.0134	(8)	0.0740	± 0.0188	(7)	0.0846	± 0.160	(38)
V_{ss}, L/kg	0.495	± 0.086	(7)	0.472	± 0.047	(8)	0.560	± 0.088	(8)	0.482	± 0.064	(8)	0.438	± 0.099	(7)	0.485	± 0.085	(38)

Table 14

Summary of Pharmacokinetic Parameters (SD)[a] for Brovinbloc and ASL-8123 Metabolite From Comprehensive Model

Parameter (units)	Subject No. 1	2	3	4	5	6	7	8	Mean[b] [SD]
V_c, L/kg									1.91 [0.62]
V_t, L/kg									1.41 [1.43]
Cl_d, L/h/kg									7.40 [5.57]
Cl, L/h/kg									22.9 [4.3]
V_M, L/kg									0.437 [0.086]
Cl_e, L/h/kg									0.0818 [0.0065]
V_{ss}, L/kg									3.32 [1.83]
MRT, h									0.138 [0.049]
$t_{1/2a}$, h									0.039 [0.013]
$t_{1/2\beta}$, h									0.220 [0.132]
Cl_m, L/h/kg									16.7 [3.4]
$t_{1/2met}$, h									3.70 [0.61]
f_m									0.732 [0.030]

[a] The first six parameters were obtained by NONLIN fitting of Eq. 7 and 13 and computer-generated standard deviations are in parentheses.

[b] Mean and [Standard Deviation] for parameters of 8 subjects.

V_c = Central volume of distribution for Brovinbloc.

V_t = Tissue volume of distribution for Brovinbloc.

Cl_d = Intercompartmental (distribution) clearance of Brovinbloc.

Cl = Total clearance of Brovinbloc.

V_M = Volume of distribution for ASL-8123.

Cl_e = Renal clearance of ASL-8123.

V_{ss} = Steady-state volume of distribution for Brovinbloc.

MRT = Mean Residence Time of Brovinbloc.

$t_{1/2a}$ = Distribution half-life of Brovinbloc.

$t_{1/2\beta}$ = Elimination half-life of Brovinbloc.

Cl_m = Formation clearance of ASL-8123 for Brovinbloc.

$t_{1/2met}$ = Elimination half-life of ASL-8123.

f_m = Fractional metabolism of Brovinbloc.

Table 15

Comparison of Actual[a] and Predicted Steady-State Brevibloc Concentrations (C_{ss})

C_{ss} (ng/ml)	Subject No. 1	2	3	4	5	6	7	8	Mean [SD]
D_0 = 50 mcg/kg/min Meas.									156 [32]
Pred.									136 [27]
D_0 = 100 Meas.									312 [145]
Pred.									271 [54]
D_0 = 150 Meas.									479 [195]
Pred.									407 [82]
D_0 = 200 Meas.									712 [278]
Pred.									542 [109]
D_0 = 300 Meas.									993 [279]
Pred.									814 [163]

[a] Measured during the occurrence of plateau Brevibloc concentrations over 60-360 min.

Table 16

Comparison of Actual[a] and Predicted Maximum ASL-8123 Metabolite Concentrations (C^{max})

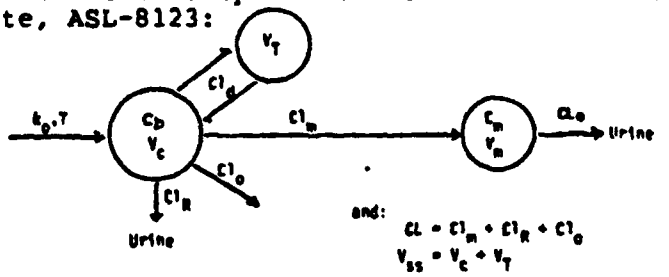
C^{max}_m (mcg/ml)	Subject No. 1	2	3	4	5	6	7	8	Mean [SD]
D_0 = 50 mcg/kg/min Meas.									17.4 [2.9]
Pred.									18.2 [2.5]
D_0 = 100 Meas.									32.4 [4.0]
Pred.									36.2 [4.9]
D_0 = 150 Meas.									64.3 [8.4]
Pred.									79.6 [6.1]
D_0 = 200 Meas.									65.9 [9.8]
Pred.									72.3 [9.9]
D_0 = 300 Meas.									124.6 [26.3]
Pred.									108.5 [14.8]

[a] Mean of 3 consecutive metabolite concentrations at the end of the infusion period.

[b] Single value at 1442 min.

Figure 1

The following pharmacokinetic model was used to characterize the disposition of Brevibloc and its metabolite, ASL-8123:



and:

$$CL = Cl_m + Cl_R + Cl_o$$

$$V_{ss} = V_c + V_T$$

where:

k_o = Zero-order infusion rate of Brevibloc (5 rates)
T = Duration of infusion (6 or 24 hours)
C_b = Blood concentration of Brevibloc
V_C = Central volume of distribution
V_T = Tissue volume of distribution
V_{ss} = Steady-state volume of distribution
Cl_d = Intercompartmental (distribution) clearance
Cl_m = Formation clearance of ASL-8123
Cl_R = Renal clearance of Brevibloc
Cl_o = Other clearance of Brevibloc
CL = Total clearance of Brevibloc
C_m = Blood concentration of ASL-8123
V_m = Volume of distribution of ASL-8123
CL_e = Renal clearance of ASL-8123
f_m = Fractional metabolism of Brevibloc (Cl_m/CL)
MRT = Mean Residence Time of Brevibloc (I.V. bolus condition)
C_{ss} = Steady-state blood concentrations of Brevibloc

Solution of the equation for blood concentrations of Brevibloc (C_b) as a function of time (t) yields:

(Eq. 7) $$C_b = \frac{k_o \cdot C_1}{\lambda_1} (e^{\lambda 1 T} - 1)\, e^{-\lambda 1 t} + \frac{k_o \cdot C_2}{\lambda_2} (e^{\lambda 2 T} - 1)\, e^{-\lambda 2 t} -$$

Figure 2

BREVIBLOC DOSE PROPORTIONALITY STUDY
MEAN OF 8 SUBJECTS

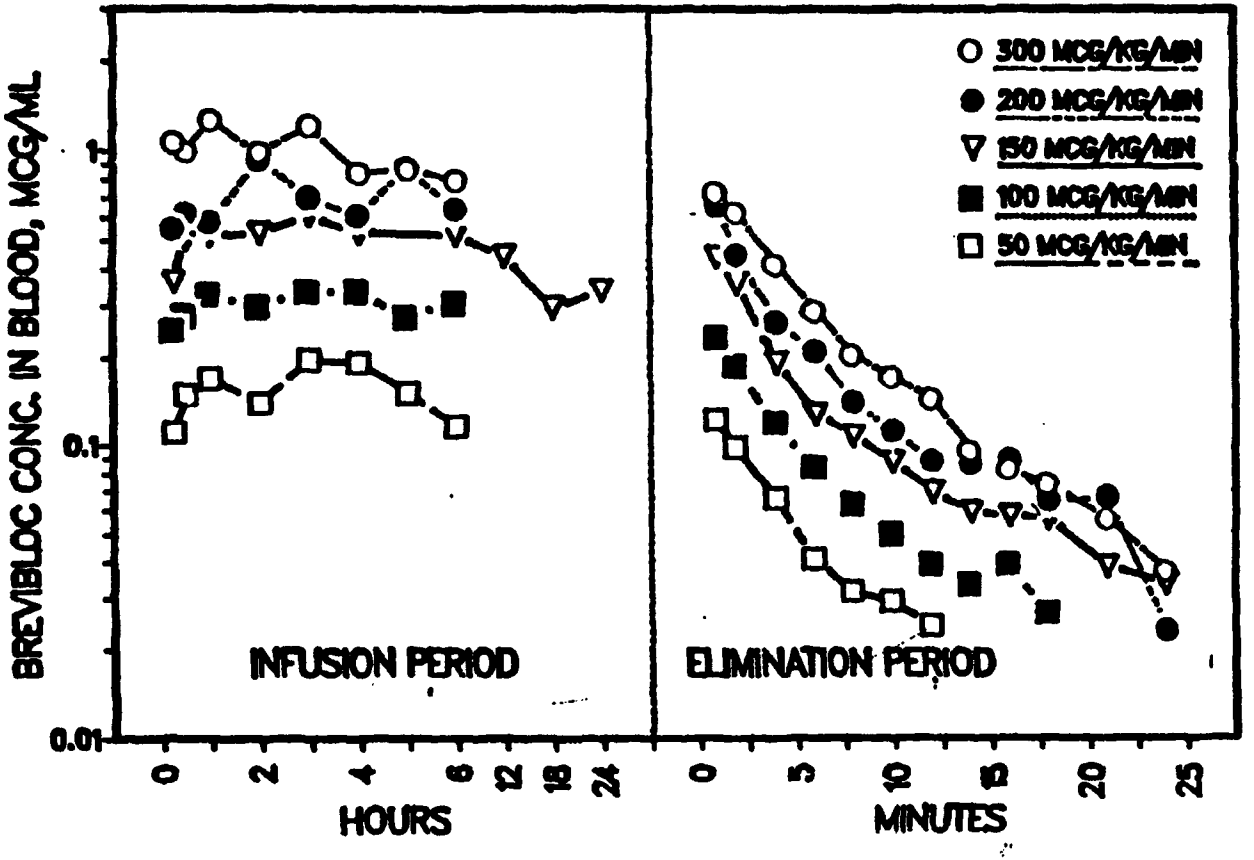


Figure 3

BREVIBLOC DOSE PROPORTIONALITY STUDY
MEAN OF 8 SUBJECTS

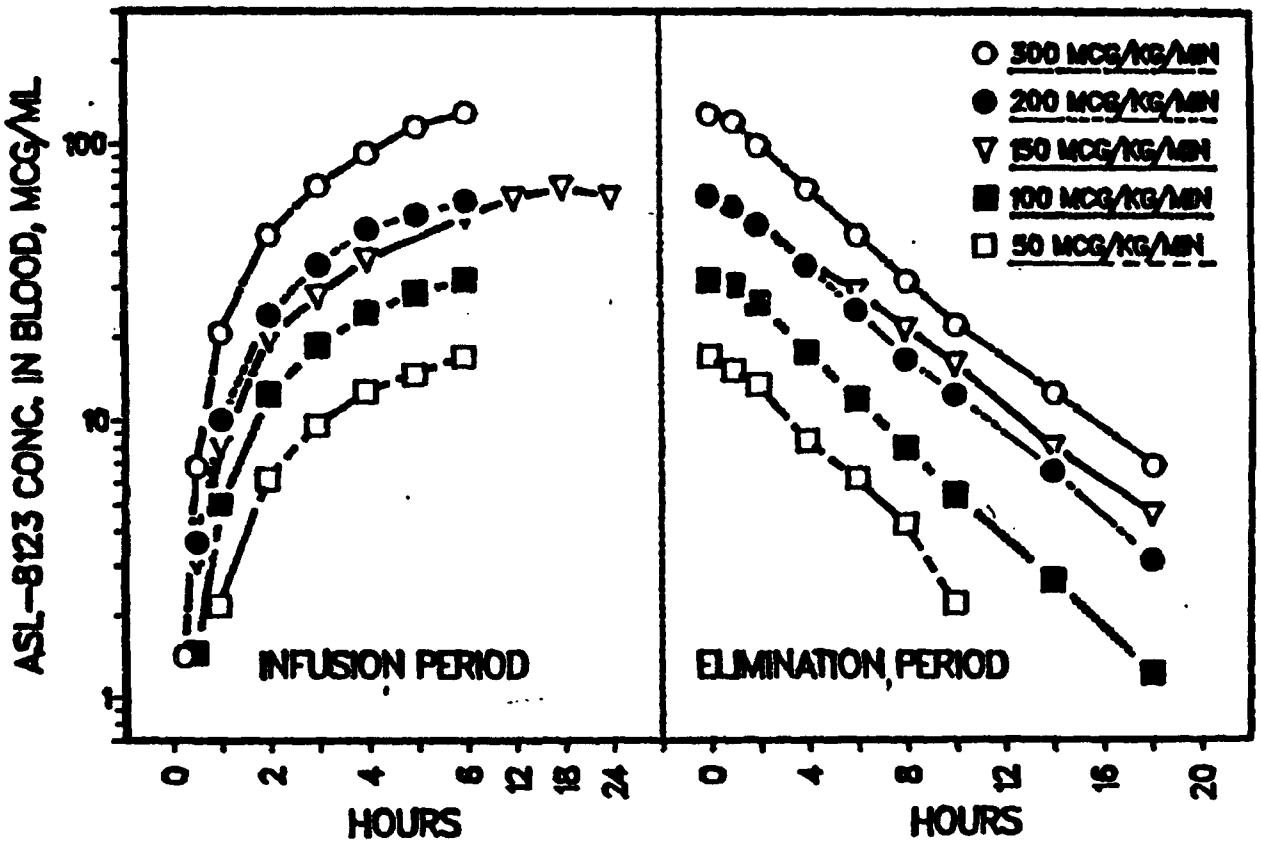


Figure 4

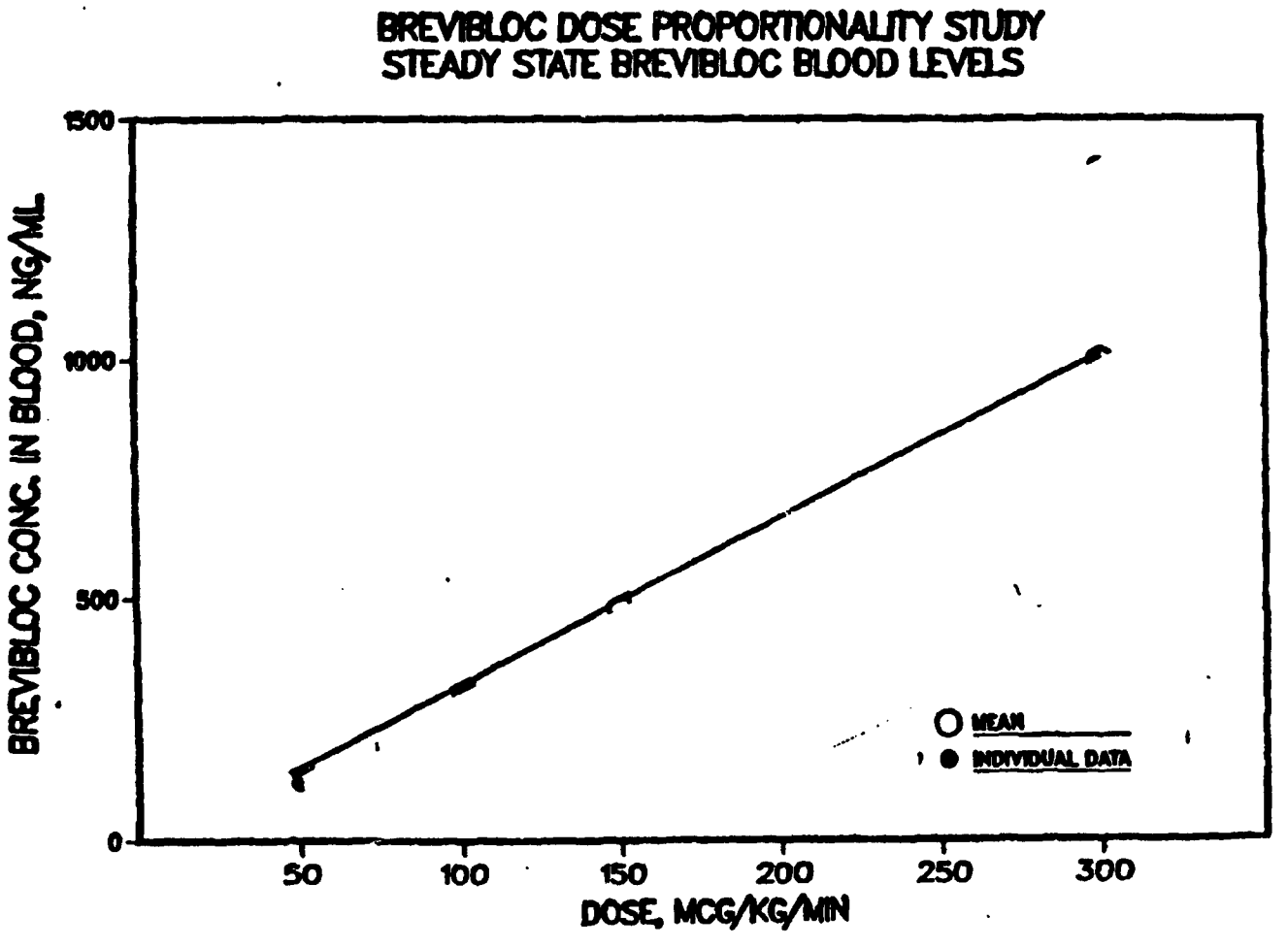
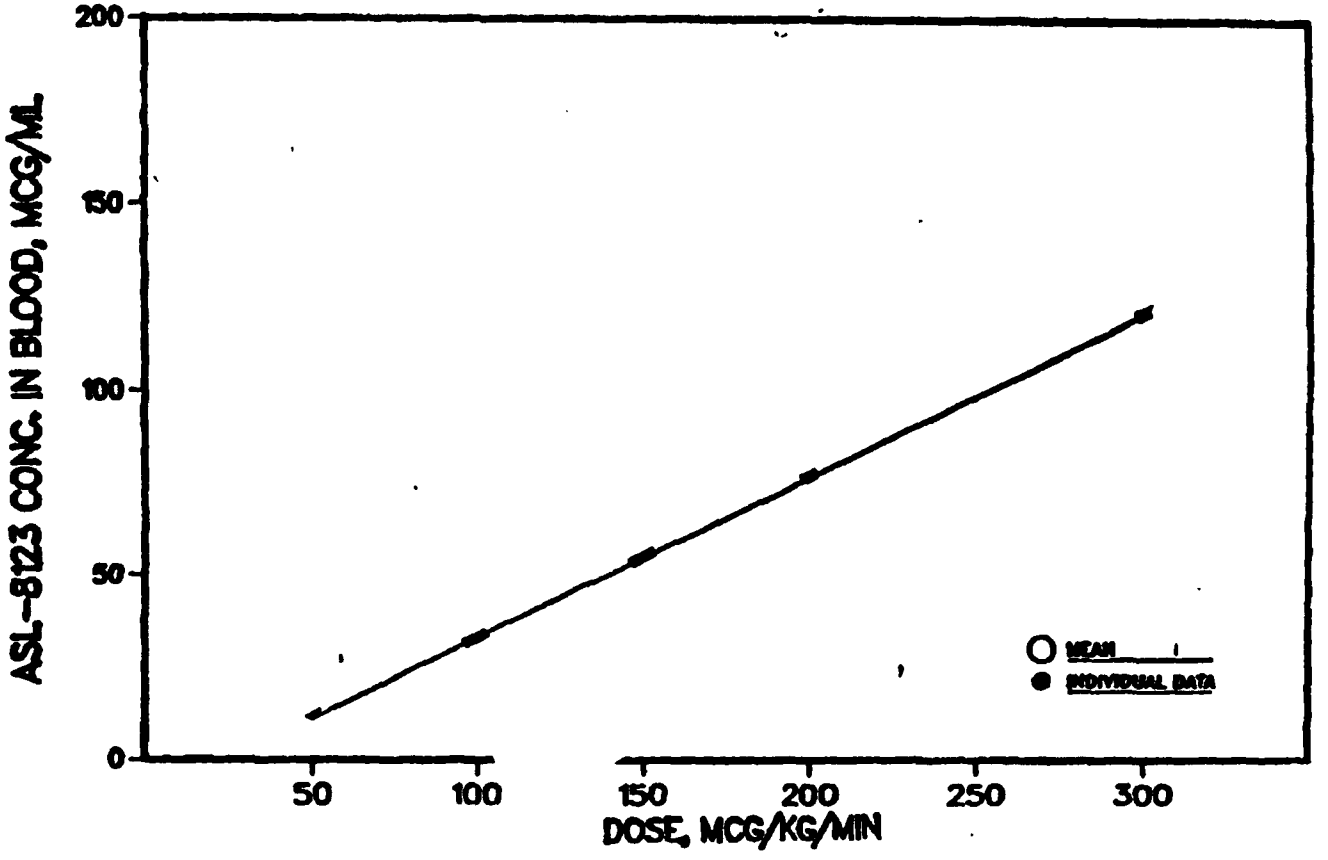

BREVIBLOC DOSE PROPORTIONALITY STUDY
STEADY STATE BREVIBLOC BLOOD LEVELS
BREVIBLOC CONC. IN BLOOD, NG/ML
1500
1000
500
0
50
100
150
200
250
300
DOSE, MCG/KG/MIN
MEAN
INDIVIDUAL DATA

Figure 5

BREVIBLOC DOSE PROPORTIONALITY STUDY
SIX HOUR ASL-8123 BLOOD LEVELS



Appendix B

– ANALYTICAL methodologies

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Appendix C

Table 1

SUMMARY OF PHARMACOKINETIC PARAMETERS OF ASL-8123

SUBJECT	INFUSION TIME	C_{ss} (pg/ml)	β (min^{-1})	$T_{1/2}$, β (min)	$AUC_{0-\infty}$ (ng·min/ml)	Total Clearance (ml/hr·kg)		Volume of Distribution (liter/kg)	
						using C_{ss}	using AUC	using C_{ss}	using AUC
201	6								
202	12								
203	24								
204	36								
205	36								
206	48								
207	48								
208	48								
209	48								
210	48								
211	48								
MEAN OF 206-211	48	69.1	0.00286	243	189819	110.3	110.1	0.039	0.037
STANDARD DEVIATION		10.8	0.00016	11.7	21917	20.0	20.9	0.007	0.006

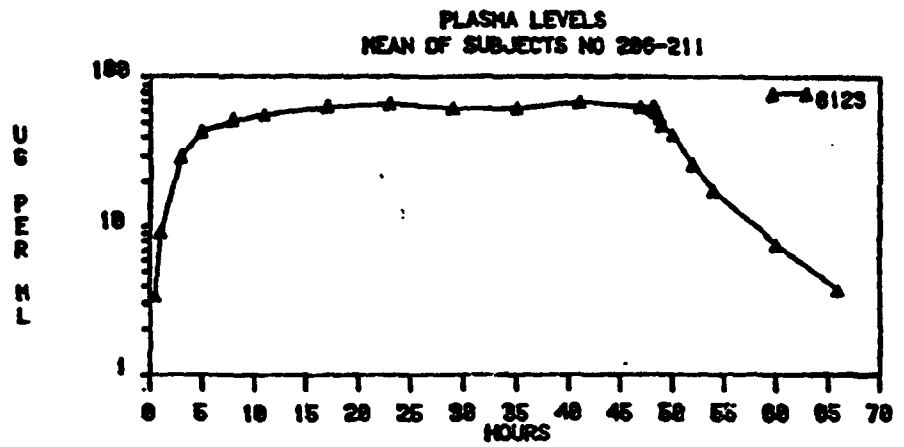
Table 2

PERCENT OF DOSE RECOVERED IN URINE

SUBJECT	INFUSION TIME (hr)	TOTAL DOSE (g)	Recovered as ASL-8052	Recovered as ASL-8123	TOTAL
201					
202					
203					
204					
205					
206					
207					
208					
209					
210					
211					
MEAN OF 206-211*			1.39	88.2	89.6
S.D.			0.23	4.89	5.01

* These subjects received the longest infusion, 48 hr. of ASL-8052. Urine was collected during the entire infusion and for 12 hours after cessation of ASL-8052 infusion.

FIGURE 1



The values plotted are means of the 6 subjects who received 48 hour infusions of ASL-8052 at 150 µg/min/kg.

Appendix D

- Digoxin interaction study

Table 4

Steady-State Blood Levels, Total Body Clearance, and Half-Life of Bravibloc After Administration of Bravibloc Alone and Bravibloc + Digoxin to Eleven Subjects

Subject	Bravibloc			Bravibloc-Digoxin		
	Steady-State Conc. C_{ss} (mcg/ml)[a]	Total Body Clearance Cl (ml/min/kg)[aa]	Half-Life $t_{1/2}$ (min)[aa]	Steady-State Conc. C_{ss} (mcg/ml)[a]	Total Body Clearance Cl (ml/min/kg)[aa]	Half-Life $t_{1/2}$ (min)[aa]
1						
2						
3						
4						
5						
6						
7						
9						
10						
11						
12						
Mean ± SD	1.57 ± 0.650	223 ± 86.2	9.6 ± 2.4	1.81 ± 0.983	231 ± 149	6.1 ± 2.6

[a] Average of 60, 120, 240, and 360 min concentrations.

[aa] Calculated using non-compartmental method.

[a] No 360 min concentration.

[b] Only 60 min concentration.

Table 22

Pharmacokinetic Parameters[a] for Brevibloc in Eleven Subjects After Administration of Brevibloc and Brevibloc + Digoxin

Treatment	Subject #	Elimination Rate Constant (min^{-1})	Half-Life (min)	Apparent Volume of Distribution (l/kg)	Total Body Clearance (ml/min/kg)
Brevibloc	1				
	2				
	3				
	4				
	5				
	6				
	7				
	9				
	10				
	11				
	12				
Mean ± S.D.		0.152 ± 0.047	5.0 ± 2.1	1.57 ± 1.48	251 ± 107
Brevibloc + Digoxin	1				
	2				
	3				
	4				
	5				
	6				
	7				
	9				
	10				
	11				
	12				
Mean ± S.D.		0.142 ± 0.049	5.4 ± 1.9	1.60 ± 1.701	222 ± 109

[a] Calculated using computer fitting of the data.

Table 5

Maximum Concentration Attained in the Blood and the Elimination Half-Life of the Metabolite, ASL-8123, After Administration of Brevibloc and Brevibloc + Digoxin

	Max. ASL-8123 Conc. in Blood (mcg/ml)		Elimination Half-Life of ASL-8123 (hr)	
Subject	Brevibloc	Brevibloc + Digoxin	Brevibloc	Brevibloc + Digoxin
1				
2				
3				
4				
5				
6				
7				
9				
10				
11				
12				
Mean ± S.D.	97.6 ± 12.0	99.3 ± 14.0	3.5 ± 0.85	3.2 ± 0.39

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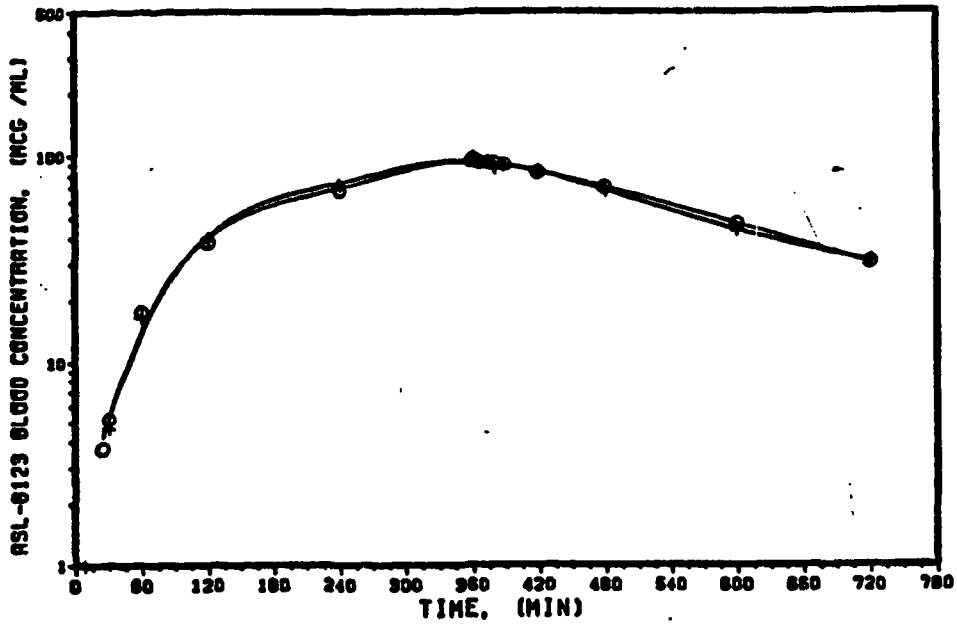

Figure 2. Average blood concentration-time profile of the metabolite, ASL-8123, after administration of Brevibloc (O) and Brevibloc + digoxin (+) to eleven subjects.

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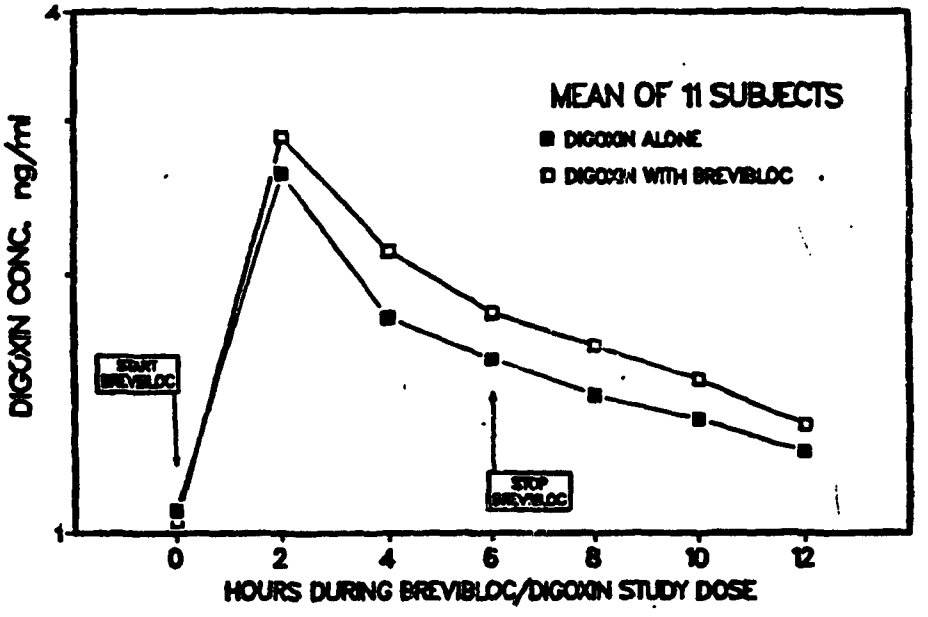

Figure 4. Average digoxin serum concentration after administration of digoxin and digoxin + Brevibloc.

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M E M O R A N D U M

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drugs and Biologics
Office of Drug Standards

DATE : JUN 27 1986

TO : Raymond Lipicky, M.D.
Acting Director, Division of Cardio-Renal Drug Products
HFN-110

FROM : Jerome P. Skelly, Ph.D.
Director, Division of Biopharmaceutics
HFN-220

SUBJECT: Esmolol HCl (Brevibloc)

Background:

Brevibloc (esmolol HCl) has a very short duration of pharmacological action because of its rapid metabolic inactivation. Animal studies show that this rapid inactivation occurs via esterase hydrolysis of the methyl ester functionality in Brevibloc to the corresponding, non-toxic, carboxylic acid (ASL-8123).
The drug is labelled for intravenous administration. Continuous infusion is required to achieve a prolonged pharmacological response. Pharmacokinetic studies of Brevibloc and ASL-8123, which is approximately 1/1500 as potent as esmolol HCl in humans provide the basis for the dosage regimen developed.

Pharmacokinetic Analysis:

Dose proportionality over a dosage range of 50-300 mcg/kg/min was established in normal subjects. Blood concentrations of methanol, a major biotransformation product, rose to 30 to 76 mcg/ml (normal is 3 to 7 mcg/ml), and were well below the toxic concentrations reported to be in the range of 1,000-3,000 mcg/ml. Formate, an oxidation product of methanol was reported to be between 3.2 and 19.1 mcg/ml. None of the formate concentrations determined in the study were reported to be above the normal range and none of the bicarbonate measurements were found to be outside the normal range (23-32 mmol/L). The overall mean percentage of the dose excreted for all doses, adjusted for the difference in mol. weight, was 0.76% and 73.2% for Brevibloc and ASL-8123, respectively.

The steady-state concentrations (Css) following an intravenous infusion were determined from the samples taken between one hour and the end of the infusion. A linear least squares regression of the relationship between Css and the dose gave a correlation coefficient of 0.82 over the dose range of 50-300 mcg/ml/min with an intercept not statistically significantly different from zero, indicating that the elimination of Brevibloc was not saturable within the study range.

Half-life estimates, were determined by linear regression of the terminal phase of the ln esmolol conc. vs. time curve. The half-life estimate was not dose-dependent and the overall mean half-life was reported to be 0.131 hours or 7.88 +/- 3.48 minutes.

Vdss had an overall mean (+/- S.D.) of 2.42 +/- 1.36 L/Kg (n=30).

The mean TBC was 20.9 +/- 8.0 L/Kg/Hr.

Infusion of esmolol was not long enough to have established the steady-state of ASL-8123 during the 6 hour infusion periods. The terminal mean half-life was 4.03 +/- 0.56 hours and was not dose dependent. The total body clearance for ASL-8123 calculated from dose and AUC data was 0.08 +/- 0.016 L/Kg/Hr. The vol. of distribution of the metabolite was 0.485 +/- 0.085 L/Kg, (n=38). The steady-state blood concentrations of both esmolol and ASL-8123 apparently increase linearly with dose, while the t1/2, Cl, and Vd for both compounds are apparently dose independent.

The suitability of the model employed by the firm to predict the distribution and elimination pharmacokinetics of Brevibloc was justified by least-squares fitting procedure to determine the absence of systematic deviation in the plateau and biexponential disposition pattern of Brevibloc and essentially zero-order rise and subsequent monoexponential decline of metabolite concentrations.

Results suggest that esmolol distributes rapidly and appreciably into tissues. The mean inter-compartmental clearance of 7.4 L/hr/kg is approximately 8.6 L/min., which is similar to cardiac output. The firm concluded that permeability of the drug into tissues is high since blood flow is the rate-limiting factor in the rate of tissue distribution of the drug. The mean estimate of the Vc (1.9 L/kg) and Vss (3.3 L/kg) suggests a moderately large distribution space of the drug.

Total systemic clearance of esmolol was obtained at steady-state. The average value of 22.9 +/- 4.3 L/hr/kg is approximately 27 L/min which markedly exceeds both liver blood flow (1.5 l/min) and cardiac output (8 L/min.) suggesting that clearance is also a function of the ester hydrolysis and is consistent with biotransformation by 'non-specific enzymes' in blood and various body tissues. The rapid clearance and large volume of distribution of esmolol account for the small time parameters of this drug. These parameters suggest that the major determinant of the duration of the drug concentrations in the body is the method of administration. With the cessation of the infusion of the drug, the mean t1/2 of the alpha phase was only 2.3 minutes, range (1.4 to 4.0 minutes), while the t1/2 of the beta phase was only 13 minutes.

The propionic acid metabolite exhibited a small mean volume of distribution (Vd_m=0.44 +/- 0.09 L/kg) and a low mean clearance (Cl_e= 0.82 +/- 0.006 L/hr/kg). These results are consistant with the behavior of weak acids which are ionized at a physiological pH, and thus do not distribute to a great extent into the intracellular space. The result is that is cleared to a large extent by the kidney (averaged 73.2 +/- 3.0% of the total dose). The Cle of ASL-8123 is moderate, 95 ml/min, and supports the premise that the clearance of this biotransformation product is dependent upon the renal function of the patient and the subject.

The parameters, in general, calculated by the non-compartmental and compartmental model methods are in good agreement. There appears to be more variability associated with pharmacokinetic parameters determined for esmolol when compared to the metabolite, not unexpected since the drug is eliminated so rapidly.

The pharmacokinetic analysis of the esmolol data demonstrated no dose dependency. There was an apparent linear relationship between dose and blood concentrations, and the elimination parameters were not affected by alterations in the dose (range 50 to 300 mcg/kg/min). The very short T1/2B and the rapid clearance of the drug from the blood (mean of 27 L/min.) greatly exceeded both liver and cardiac output suggesting that the drug is hydrolyzed extensively within the blood and surrounding tissues.

The pharmacokinetic analysis of the principle metabolite, ASL-8123 (propionic acid metabolite), demonstrated dose independent pharmacokinetics. The renal clearance of ASL-8123 is approximately 95 ml/min which is slightly less than the GFR in normal men, (approximately 131 ml/min.) suggesting that passive diffusion of the biotransformation product plays an important role in the renal metabolite excretion. Kidney dysfunction is not expected to be a problem with the metabolite since it is not considered to be toxic (according to Gorden Johnson, pharmacologist in Cardio-Renal) and the fact that the drug is not intended to be administered intravenously for long periods of time.

The firm has reported uncompleted interim studies describing the disposition of the drug and metabolite in hepatic and renal dysfuntion individuals. Since the labeling claim based on this unsubmitted information indicates a 10 fold increase in metabolite elimination half-life in patients with end stage renal disease, the data should be submitted and reviewed.

Digoxin Interaction Study:

The post-infusion Brevibloc blood concentration vs. time data were described by a one term polyexponential equation following a 6 hour infusion of Brevibloc. The T1/2 of Brevibloc averaged 5.6 minutes after Brevibloc and 6.1 minutes after Brevibloc-digoxin treatments. There were no statistically significant differences ($p|0.05$) between the two treatments.

The concentrations of Brevibloc after the administration of Brevibloc plus digoxin increased in 7 subjects while the concentrations decreased in 4 subjects. Means were not significantly different ($p|0.05$) between the two treatments with the mean Css of 1.57 and 1.81 ug/ml following administration of Brevibloc and Brevibloc-digoxin, respectively.

Total body clearance of Brevibloc after Brevibloc-digoxin treatment were generally lower compared to those after Brevibloc alone. Non-compartmental analysis showed statistically significant differences ($p|0.05$) in the mean clearances between the two treatments. The mean total body clearances were 223 and 231 ml/min/kg after administration of Brevibloc and Brevibloc-digoxin, respectively.

Total body clearance of Brevibloc calculated using the nonlinear computer fitting of the data showed that the clearance varied considerably among subjects and between the two treatments. The difference between the means (251 and 222 ml/min/kg after Brevibloc and Brevibloc-digoxin treatments, respectively) was not statistically significant (p 0.05).

Clearance of Brevibloc did not appear to be affected by the co-administration of the digoxin. The large estimate of VdB for Brevibloc suggests a rapid elimination of Brevibloc and also of the extravascular distribution of the drug. The limited urinary excretion data suggested that the parent drug was extensively biotransformed and eliminated extensively by the non-renal route.

There was a lack of statistically significant differences in the t1/2, Cmax of the metabolite, ASL-8123, between the two treatments, suggesting that the pharmacokinetic disposition is not influenced by the co-administration of digoxin. There were no significant differences in digoxin peak serum concentration or in the time to reach the peak concentration.

Labelling:

The firm has presented labelling which states that the pharmacokinetics of Brevibloc have been evaluated in patients with hepatic disease and end-stage renal disease. The claim states that the pharmacokinetic profiles were unchanged in these patients compared to those in normal subjects. In a conversation between the Division of Biopharmaceutics' Dr. Donald L. Heald and the Director of Regulatory Affairs, Lee Possley, the Division was informed that the firm had just completed the work on these studies and was in the process of reviewing the results. Since the Division of Biopharmaceutics lacks substantiation for these claims at this time, it is unable to make any recommendation concerning them. The point is called to the attention of the reviewing medical officer.

Overall Conclusion:

1. The firm has defined the pharmacokinetic profile of the short acting beta-blocker, esmolol HCl and its biotransformation product, ASL-8123."

2. The firm, without submitting corraboration data, indicated that compared to normal subjects, the pharmacokinetics of the acid metabolite was significantly different in patients with renal disease in that the elimination half-life was increased about
ten times that in normals, and the plasma levels were considerably elevated."

Recommendation:

The bioavailability study conducted by American Critical Care on its esmolol HCl IV injection, 100 mg/ml strength is approvable from the biopharmaceutics point of view. Since no data were submitted to document the increased metabolite plasma half-life, the Division is unable to make any recommendation in this regard. We call this to the attention of the reviewing medical officer.

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