CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-873

CHEMISTRY REVIEW(S)

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

1. **NDA:#** 20-873 **2. CHEM REVIEW #** 5 **3. REVIEW DATE:** November 14, 2000

4. APPLICATION HISTORY

SUBMISSIONS REVIEWED

	DOCUMENT
Amendment BC	06-Apr-2000
Amendment BZ	17-Jul-2000
Amendment BL	09-Oct-2000
Amendment BC	09-Nov-2000

PREVIOUS DOCUMENTS

DOCUMENT TYPE	DATE	COMMENT
Original	23-Dec-97	IR letter sent 11-Jul-98
Amendment BZ	31-Jan-98	SAS Stability Diskettes
Amendment BZ	25-Feb-98	Response to 11-Feb-98 IR Letter
Amendment BC	28-Jul-98	Batch Records
Amendment BZ	20-Aug-98	Batch Records
Amendment BC	06-Oct-98	Revised anti-thrombin assay
Correspondence	13-Oct-98	Change in tradename
Chem. Review #1	30-Oct-98	
NA Letter	18-Nov-98	
Resubmission	22-Apr-99	Class 2
Chem Review #2	23-Jul-99	Review of batch data for bioequivalence
Amendment	17-Sep-99	
Chem Review #3	06-Oct-99	
AE Letter	28-Oct-99	
Amendment BZ Resubmission (Class 2)	11-Nov-99	
Amendment BL	24-Feb-00	
Amendment BC	30-Mar-00	
Chem Review #4	12-Apr-00	
AE letter	11-May-00	

5. NAME & ADDRESS OF APPLICANT:

The Medicines Company
One Cambridge Center
Cambridge MA 02142

6. DRUG PRODUCT NAME:

Proprietary:	Angiomax (originally Hirulog)
Nonproprietary/USAN:	bivalirudin
Chem.Type/Ther.Class:	1S
Code names:	SF071 (UCB Bioproducts code) BG8967 (Biogen code)

7. PHARMACOLOGICAL CATEGORY: antithrombotic

8. INDICATION: anticoagulant for patient undergoing percutaneous transluminal angioplasty (PTCA)

9. DOSAGE FORM: powder for injection

10. STRENGTH: 250 mg

11. **ROUTE OF ADMINISTRATION:** intravenous

12. **HOW DISPENSED:** __X__ Rx ___OTC

13. **SPOTS:** ____Yes __X__ No

14. **CHEMICAL IDENTIFICATION:** D-phe-L-pro-L-arg-L-pro-gly-gly-gly-gly-L-asn-gly-L-asp-L-phe-L-glu-L-glu-L-ile-L-pro-L-glu-L-glu L-tyr-L-leu trifluoroacetate hydrate
(D)FPRPGGGGNGDFEEIPEEYL
CAS number: 128270-60-0

15. **SUPPORTING DOCUMENTS:**

DMF	Holder	Type	Title	Date of LOA	Status
		II		December 18, 1997	Adequate Review October 12, 2000
		III		November 4, 1997	Adequate Review, Sept 24, 1998
		V		November 4, 1997	N/A

16. **RELATED DOCUMENTS**

17. **CONSULTS:**

Microbiology: Approvable Reviews dated May 17, 1999 and September 16, 1999. **ACCEPTABLE**

OPDRA has found the name **ACCEPTABLE**. However there may be some concerns from DDMAC.

18. **REMARKS/COMMENTS:** The applicant has provided corrected assay procedures.

19. **CONCLUSIONS & RECOMMENDATIONS:** The NDA may be APPROVED.

/S/ Nov 14, 2000

Arthur B. Shaw, Ph.D.
Review Chemist HFD-180

/S/ 11/14/00
Liang Zhou, Ph.D.
Chemistry Team Leader, HFD-180

in DFS 11/14/00

cc:
NDA 20-873
HFD-180/Division File/NDA 20-873
HFD-181/CSO
HFD-180/LTalarico
HFD-180/LZhou
HFD-180/KRobiesuh
HFD-180/AShaw
R/D Init by: LZhou 14-Nov-2000

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DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

1. **NDA:#** 20-873 2. **CHEM REVIEW #** 4 3. **REVIEW DATE:** April 1, 2000

4. **APPLICATION HISTORY**

SUBMISSIONS REVIEWED

	DOCUMENT	CDER
Amendment BZ Resubmission (Class 2)	11-Nov-1999	12-Nov-1999
Amendment BL	24-Feb-2000	25-Feb-2000
Amendment BC	30-Mar-2000	31-Mar-2000

PREVIOUS DOCUMENTS

DOCUMENT TYPE	DATE	COMMENT
Original	23-Dec-97	IR letter sent 11-Jul-98
Amendment BZ	31-Jan-98	SAS Stability Diskettes
Amendment BZ	25-Feb-98	Response to 11-Feb-98 IR Letter
Amendment BC	28-Jul-98	Batch Records
Amendment BZ	20-Aug-98	Batch Records
Amendment BC	06-Oct-98	Revised anti-thrombin assay
Correspondence	13-Oct-98	Change in tradename
Chem. Review #1	30-Oct-98	
NA Letter	18-Nov-98	
Resubmission	22-Apr-99	Class 2
Chem Review #2	23-Jul-99	Review of batch data for bioequivalence
Amendment	17-Sep-99	
Chem Review #3	06-Oct-99	
AE Letter	28-Oct-99	

5. **NAME & ADDRESS OF APPLICANT:**

The Medicines Company
One Cambridge Center
Cambridge MA 02142

6. **DRUG PRODUCT NAME:**

Proprietary: Angiomax (originally Hirulog)
Nonproprietary/USAN: bivalirudin
Chem.Type/Ther.Class: 1S
Code names: SF071 (UCB Bioproducts code)
BG8967 (Biogen code)

7. **PHARMACOLOGICAL CATEGORY:** antithrombotic

8. **INDICATION:** anticoagulant for patient undergoing percutaneous transluminal angioplasty (PTCA)

9. **DOSAGE FORM:** powder for injection

10. **STRENGTH:** 250 mg

11. **ROUTE OF ADMINISTRATION:** intravenous

12. **HOW DISPENSED:** X Rx ___OTC

13. **CHEMICAL IDENTIFICATION:** D-phe-L-pro-L-arg-L-pro-gly-gly-gly-gly-L-asn-gly-L-asp-L-phe-L-glu-L-glu-L-ile-L-pro-L-glu-L-glu L-tyr-L-leu trifluoroacetate hydrate

(D)FPRPGGGGNGDFEEIPEEYL
CAS number: 128270-60-0

14. **SUPPORTING DOCUMENTS:**

DMF	Holder	Type	Title	Date of LOA	Status
	ICTS	II		December 18, 1997	Inadequate Review and Letter April 11, 2000
		III		November 4, 1997	Adequate Review, Sept 24, 1998
		V		November 4, 1997	N/A

15. **RELATED DOCUMENTS**

16. **CONSULTS:** Microbiology: Approvable Reviews dated May 17, 1999 and September 16, 1999.
Labeling and Nomenclature Committee New name Angiomax (May 14, 1999)

17. **REMARKS/COMMENTS:** The applicant has provided corrected assay procedures. There are a few outstanding issues concerning in-process controls, update of assay procedures, and labeling.

18. **CONCLUSIONS & RECOMMENDATIONS:** Approvable (AE) pending

a. resolution of outstanding issues in [redacted]
b. response to information requests in Section H.
c. Satisfactory establishment inspections

/S/ April 12, 2000
Arthur B. Shaw, Ph.D.
Review Chemist HFD-180

/S/ 4/12/00
Liang Zhou, Ph.D.
Chemistry Team Leader, HFD-180

cc:
NDA 20-873
HFD-180/Division File/NDA 20-873
HFD-181/CSO
HFD-180/LTalarico
HFD-180/Lzhou
HFD-180/KRobiesuh
HFD-180/AShaw
R/D Init by: LZhou 10-Apr-2000

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OCT - 7 1999

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

1. **NDA:#** 20-873 2. **CHEM REVIEW #** 3 3. **REVIEW DATE:** October 5, 1999

4. **APPLICATION HISTORY**

SUBMISSIONS REVIEWED

	DOCUMENT	CDER
Resubmission (Class 2)	22-Apr-99	22-Apr-99
Amendment	17-Sep-99	21-Sep-99

PREVIOUS DOCUMENTS

DOCUMENT TYPE	DATES DOCUMENT	CDER	ASSIGNED	
Original	23-Dec-97	23-Dec-97	30-Dec-97	IR letter sent 11-Jul-98
Amendment BZ	31-Jan-98	04-Feb-98	12-Feb-98	SAS Stability Diskette
Amendment BZ	25-Feb-98	27-Feb-98	17-Mar-98	Response to 11-Feb-98 IR Letter
Amendment BC	28-Jul-98	29-Jul-98	13-Aug-98	Batch Records
Amendment BZ	20-Aug-98	24-Aug-98	28-Aug-98	Batch Records
Amendment BC	06-Oct-98	07-Oct-98	19-Oct-98	Revised anti-thrombin assay
Correspondence	13-Oct-98	14-Oct-98	19-Oct-98	Change in tradename
Chem. Review #1	02-Nov-98			
NA Letter	18-Nov-98			

5. **NAME & ADDRESS OF APPLICANT:**

The Medicines Company
One Cambridge Center
Cambridge MA 02142

6. **DRUG PRODUCT NAME:**

Proprietary: Angiomax (originally Hirulog)
Nonproprietary/USAN: bivalirudin
Chem.Type/Ther.Class: 1S
Code names: SF071 (UCB Bioproducts code)
BG8967 (Biogen code)

7. **PHARMACOLOGICAL CATEGORY:** antithrombotic

8. **INDICATION:** anticoagulant for patient undergoing percutaneous transluminal angioplasty (PTCA)

9. **DOSAGE FORM:** powder for injection

10. **STRENGTH:** 250 mg

11. **ROUTE OF ADMINISTRATION:** intravenous

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(D)FPRPGGGGNGDFEEIPEEYL
CAS number: 128270-60-0

14. **SUPPORTING DOCUMENTS:**

DMF	Holder	Type	Title	Date of LOA	Status
[redacted]		II	[redacted]	December 18, 1997	Inadequate Review 30-Sep-99 Letter 01-Oct-99
		III		November 4, 1997	Adequate Review, Sept 24, 1998
		V		November 4, 1997	N/A

15. **RELATED DOCUMENTS** [redacted]

16. **CONSULTS:** Microbiology: Approvable Reviews dated May 17, 1999 and September 16, 1999.
Labeling and Nomenclature Committee New name Angiomax (May 14, 1999)

17. **REMARKS/COMMENTS:** The DMF for the bulk drug [redacted] still has some outstanding issues. The drug product manufacturing is now acceptable. The calculations for the [redacted] assay for impurities needs changes to ensure that impurities can be

picked up on stability testing. See "Deficiencies" under H. Establishment inspections still outstanding. At the present time, there is insufficient stability data for the drug product manufactured using the current procedure, using suitable stability-indicating assays and reporting procedures, to assign an expiration date.

18. **CONCLUSIONS & RECOMMENDATIONS:** Approvable (AE) pending

a. resolution of outstanding issues in DMF [redacted]
b. response to deficiencies in Section H.
c. Satisfactory establishment inspections

A post-approval commitment may satisfy a. and b.

/S/ 10/6/99
Arthur B. Shaw, Ph.D.
Review Chemist HFD-180

/S/ 10/7/99
Liang Zhou, Ph.D.
Acting Chemistry Team Leader, HFD-180

cc:
NDA 20-873
HFD-180/Division File/NDA 20-873
HFD-181/CSO
HFD-180/LTalarico
HFD-180/Lzhou
HFD-180/KRobiesuh
HFD-180/AShaw
R/D Init by: EDuffy 04-Oct-1999

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OCT - 1 1999

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

1.NDA:# 20-873 **2. CHEM REVIEW #** 2 **3.REVIEW DATE:** October 1, 1999

4. SUBMISSIONS REVIEWED

	DOCUMENT	CDER	Applicant's Number	Contents
Amendment BC	22-Jun-99	23-Jun-99	23	Data to support BE
Amendment BZ	15-Sep-99	16-Sep-99	26	Chromogenic assay and mannitol assay results
Amendment BC	16-Sep-99	20-Sep-99	27	Minor questions
Amendment BC	17-Sep-99	20-Sep-99	28	Batch Record for 67A01Q
Amendment BC	17-Sep-99	20-Sep-99	29	Impurities
Amendment BC	17-Sep-99	20-Sep-99	30	
Amendment BC	20-Sep-99	21-Sep-99	31	Batch Record for 67A02Q
Amendment BC	21-Sep-99	23-Sep-99	32	Comparison of batch release for 67A01Q, 67A04Z, 67A02Q. Peptide concentration in TI Assay
Amendment BC	24-Sep-99	27-Sep-99	33	
Amendment BC	24-Sep-99	28-Sep-99	34	Comparison of 67A01Q, 67A02Q and 1020152. Second largest impurity, total impurities

5. NAME & ADDRESS OF APPLICANT:
The Medicines Company
One Cambridge Center
Cambridge MA 02142

6. DRUG PRODUCT NAME:
Proprietary: Angiomax (originally Hirulog)
Nonproprietary/USAN: bivalirudin
Chem.Type/Ther.Class: 1S
Code names: SF071 (UCB Bioproducts code)
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(D)FPRPGGGGNGDFEEIPEEYL
CAS number: 128270-60-0

14. **SUPPORTING DOCUMENTS:** N/A

15. **RELATED DOCUMENTS** ———

16. **CONSULTS:** N/A

17. **REMARKS/COMMENTS:** This review concerns only the formulations involved in the bioequivalence study.

18. **CONCLUSIONS & RECOMMENDATIONS:** The formulations ——— (frozen) used in the pivotal clinical trials and in bioquivalence study CS93316 is chemically equivalent, to Lot ——— (lyophilized) used in Study C93316. In addition, Lot ——— (lyophilized) manufactured by the process to be marketed, is chemically equivalent to the other two lots.

/S/ 10/1/99
Arthur B. Shaw, Ph.D.
Review Chemist HFD-180

/S/ 10/1/99
Liang Zhou, Ph.D.
Acting Chemistry Team Leader,
HFD-180

cc:
NDA 20-873
HFD-180/Division File/NDA 20-873
HFD-181/CSO
HFD-180/LTalaricc
HFD-180/LZhou
HFD-181/JDubeau
HFD-180/KRobie-Suh
HFD-880/JHunt
HFD-180/AShaw
R/D Init by: Lzhou 01-Oct-1999

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DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

1. **NDA:#** 20-873 **2. CHEM REVIEW #** 1 **3. REVIEW DATE:** October 30, 1998

4. APPLICATION HISTORY

DOCUMENT TYPE	DATES DOCUMENT	CDER	ASSIGNED	
Original	23-Dec-97	23-Dec-97	30-Dec-97	IR letter sent 11-Jul-98
Amendment BZ	31-Jan-98	04-Feb-98	12-Feb-98	SAS Stability Diskettes
Amendment BZ	25-Feb-98	27-Feb-98	17-Mar-98	Response to 11-Feb-98 IR Letter
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Amendment BZ	20-Aug-98	24-Aug-98	28-Aug-98	Batch Records
Amendment BC	06-Oct-98	07-Oct-98	19-Oct-98	Revised anti-thrombin assay
Correspondence	13-Oct-98	14-Oct-98	19-Oct-98	Change in tradename

NOV - 2 1998

5. NAME & ADDRESS OF APPLICANT:

The Medicines Company
One Cambridge Center
Cambridge MA 02142

6. DRUG PRODUCT NAME:

Proprietary: Angiomax (originally Hirulog)
Nonproprietary/USAN: bivalirudin
Chem.Type/Ther.Class: 1S
Code names: SF071 (UCB Bioproducts code)
BG8967 (Biogen code)

7. PHARMACOLOGICAL CATEGORY: antithrombotic

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12. HOW DISPENSED: X Rx ___OTC

13. CHEMICAL IDENTIFICATION: D-phe-L-pro-L-arg-L-pro-gly-gly-gly-gly-L-asn-gly-L-asp-L-phe-L-glu-L-glu-L-ile-L-pro-L-glu-L-glu L-tyr-L-leu trifluoroacetate hydrate

(D) FPRPGGGGNGDFEEIPEEYL
CAS number: 128270-60-0

14. SUPPORTING DOCUMENTS:

DMF	Holder	Type	Title	Date of LOA	Status
[redacted]		II	[redacted]	December 18, 1997	Inadequate Review 30-Sep-98 Letter 06-Oct-98
		III		November 4, 1997	Adequate Review, Sept 24, 1998
		V		November 4, 1997	N/A

15. RELATED DOCUMENTS [redacted]

16. CONSULTS: Microbiology: Not approvable Review dated April 8, 1998.
Labeling and Nomenclature Committee for new name Oct 16, 1998

17. REMARKS/COMMENTS: The IND for this drug was originally submitted in 1991 by Biogen. In the course of development, there were a number of communications with Biogen regarding the biological assay (thrombin inhibition test). These were not replied to satisfactorily. Biogen dropped the development of this drug in 1994. It was then picked up by The Medicines Company (TMC). All the development of the drug was by Biogen. Manufacturing of the drug substance has continued to be performed by [redacted] Most of the recent batches of drug product were manufactured by [redacted], which will manufacture the commercial product. However the lots used for the pivotal clinical trials were manufactured by Biogen.

Biogen had proposed to use the thrombin-inhibition assay (TIA)

for identity. TMC was informed that the TIA was necessary as a release specification. TMC informed the Agency that they were unable to reproduce the TIA. Attempts to validate the TIA were reported under the IND.

— has not successfully manufactured a scaled-up batch of the drug product. Attempts to do this to prepare lots for future clinical trials were unsuccessful, a fact discovered during an inspection of — Subsequent meetings and discussions with TMC and — have led to a number of proposals for the TIA and a new manufacturing procedure. The new manufacturing procedure has not been submitted to the NDA.

18. CONCLUSIONS & RECOMMENDATIONS: The application is Not Approvable. The major deficiencies are the lack of a properly validated manufacturing procedure and failure to provide a stability-indicating assay.

/S/ 10/30/98
Arthur B. Shaw, Ph.D.
Review Chemist HFD-180

/S/ 11/2/98
Eric Duffy, Ph.D.
Chemistry Team Leader, HFD-180

cc:
NDA 20-873
HFD-180/Division File/NDA 20-873
HFD-181/CSO
HFD-180/LTalarico
HFD-180/EDuffy
HFD-180/AShaw
R/D Init by: **EDuffy 10-30-98**

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