CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020884

CHEMISTRY REVIEW(S)

MAY 11 1999

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA 20-884 **CHEM REVIEW: #1** **REVIEW DATE:** May 6, 1999

SUBMISSION TYPE	DOCUMENT	DATES CDER	ASSIGNED	REVIEW
Original	Dec 15, 1998	Dec 15, 1998	Jan 7, 1999	
BC Amendment 001	Jan 13, 1999	Jan 14, 1999	Noted. NAI	Establishment Information
BZ Amendment 002	Jan 14, 1999	Jan 20, 1999	Jan 1, 1999	Executed Batch records.
BZ Amendment 003	Jan 18, 1999	Jan 19, 1999	Feb 2, 1999	Overall index, SAS transport . NAI
BC Amendment 006	Jan 29, 1999	Feb 1, 1999	Feb 4, 1999	Statistical Analysis stability data
BZ Amendment 007	Jan 29, 1999	Feb 1, 1999	Feb 4, 1999	Additional Tables
BZ Amendment 009	Feb 12, 1999	Feb 16, 1999	Feb 22, 1999	Noted NAI. Additional information on Bulk drug batches
C Amendment 010	Feb 25, 1999	Feb 26, 1999	Mar 8, 1999	Noted NIA. DMF
BC Amendment 012	Mar 11, 1999	Mar 12, 1999	Mar 16, 1999	Revised stability data
BC Amendment 013	Mar 12, 1999	Mar 15, 1999	Mar 29, 1999	Corrected electronic files. Replaces some files of amendment 006.
BZ Amendment 018	May 5, 1999	May 6, 1999	May 7, 1999	CRC issues

NAME & ADDRESS OF APPLICANT:
Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Rd./ P.O. Box 368
Ridgefield, CT 06877-0368

DRUG PRODUCT NAME:

Proprietary:	Aggrenox™ (Extended Release Capsules)
Nonproprietary/USAN:	Dipyridamole 200mg /Aspirin 25 mg
Code Name/#:	Dipyridamole: RA-8-BS
Chem.Type/Ther.Class:	Type P

PHARMACOLOGICAL CATEGORY: Combination anti-platelet agent intended for oral administration.

INDICATION:

DOSAGE FORM:	Capsule
STRENGTH:	200 mg Dipyridamole / 25 mg Aspirin
ROUTE OF ADMINISTRATION:	Oral
HOW DISPENSED:	Rx _

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
Dipyridamole: 2,6-Bis-(diethanolamino)-4,8,-dipiperidinopyrimido-[5,4-d]-pyrimidine

Aspirin: Benzoic acid, 2-(acetyloxy)-salicylic acid acetate.

Note: Refer to the Drug Substance section for structures.

SUPPORTING DOCUMENTS:

DMF Number	Item referenced	Holder	Status	Review Date	Letter Date

CONSULTS:

REMARKS/COMMENTS:

There is no applicable patent, although an application is PENDING (Vol. 1.002 page 14).
The company claims exclusivity under the provisions of 37 CFR 314.1089b)(4).
As of October 1998, Asasantine™ (dypyridamole/aspirin) Extended release capsules has received marketing approval in ___ countries.
Marketing approval is pending in ___ additional countries.

CONCLUSIONS & RECOMMENDATIONS:
This application is approvable pending the review of additional information requested, update of deficient DMF's and resolution of issues related to the plant inspections.

/S/ 5/11/99
Maria Elena Ysern, MSc
Review Chemist, HFD-180

APPEARS THIS WAY
ON ORIGINAL

/S/ 5/11/99
Eric P.Duffy, Ph.D.
Chemistry Team Leader, HFD-180

cc:
NDA 20-884
HFD-180/LTalarico
HFD-180/Div File/NDA 20-884
HFD-180/EDuffy
HFD-180/MYsern
HFD-181/JDubeau
R/D Init by: EDuffy/5-7-99
MY/dob F/T 5-7-99/WORD: n:\wordfiles\chem\N\20884901.2MY

APPEARS THIS WAY
ON ORIGINAL

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA 20-884 **CHEM REVIEW**: #3 **REVIEW DATE**: May 6, 1999

SUBMISSION TYPE	DOCUMENT	DATES CDER	ASSIGNED
Amendment/018	May 5, 1999	May 7, 1999	May 7, 1999
Amendment/019	May 19, 1999	May 20, 1999	Jun 1, 1999
Amendment/020	May 27, 1999	May 27, 1999	Jun 4, 1999

JUN - 8 1999

NAME & ADDRESS OF APPLICANT:
Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Rd./ P.O. Box 368
Ridgefield, CT 06877-0368

DRUG PRODUCT NAME:

Proprietary:	Aggrenox™ (Extended Release Capsules)
Nonproprietary/USAN:	Dipyridamole 200mg /Aspirin 25 mg
Code Name/#:	Dipyridamole: RA-8-BS
Chem.Type/Ther.Class:	Type P

PHARMACOLOGICAL CATEGORY: Combination anti-platelet agent intended for oral administration.

INDICATION:

DOSAGE FORM:	Capsule
STRENGTH:	200 mg Dipyridamole / 25 mg Aspirin
ROUTE OF ADMINISTRATION:	Oral
HOW DISPENSED:	Rx _

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
Dipyridamole: 2,6-Bis-(diethanolamino)-4,8,-dipiperidinopyrimido-[5,4-d]-pyrimidine

Aspirin: Benzoic acid, 2-(acetyloxy)-salicylic acid acetate.
Note: Refer to the Drug Substance section for structures.

SUPPORTING DOCUMENTS: See review #1.

CONSULTS:

REMARKS/COMMENTS:
The company submitted an **Amendment 018,** in May 5, 1999 (see review #1). The letter was in regard to their agreement with the Consumer Product Safety Commission concerning the Child resistant Closure (CRC

Amendment 019 includes the response from the Consumer Product Safety Commission (CPSC) to Boehringer Ingelheim in reference to the request for a temporary exemption from the requirements for child resistant packaging for Aggrenox capsules.

Amendment 020 includes a copy of the response to the CPSC in which Boehringer Ingelheim describes how they plan to implement the interim solution proposed by the Commission.

CONCLUSIONS & RECOMMENDATIONS: Information provided by the company is noted. The company will be asked in the action letter to provide a copy of the proposed revised carton which has the proposed statement concerning re-dispensing the product from a noncompliant bottle to a compliant CRC bottle.

/S/ 6/8/99
Maria Elena Ysem, MSc
Review Chemist, HFD-180

APPEARS THIS WAY
ON ORIGINAL

/S/ 6/8/99
Eric P.Duffy, Ph.D.
Chemistry Team Leader, HFD-180

cc:
NDA 20-884
HFD-180/LTalarico
HFD-180/Div File/NDA 20-884
HFD-180/EDuffy
HFD-180/MYsem
HFD-181/JDubeau
R/D Init by: EDuffy/6-8-99
MY/dob F/T 6-8-99/WORD: n:\wordfiles\chem\N\20884901.3MY

APPEARS THIS WAY
ON ORIGINAL

Draft Chem

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DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA 20-884 **CHEM REVIEW: #4** **REVIEW DATE:** Nov 2, 1994

SUBMISSION TYPE	DOCUMENT	DATES CDER	ASSIGNED	REVIEW
Original	Dec 15, 1998	Dec 15, 1998	Jan 7, 1999	
BC Amendment 001	Jan 13, 1999	Jan 14, 1999	Noted. NAI	Establishment Information
BZ Amendment 002	Jan 14, 1999	Jan 20, 1999	Jan 1, 1999	Executed Batch records.
BZ Amendment 003	Jan 18, 1999	Jan 19, 1999	Feb 2, 1999	Overall index, SAS transport . NAI
BC Amendment 006	Jan 29, 1999	Feb 1, 1999	Feb 4, 1999	Statistical Analysis stability data
BZ Amendment 007	Jan 29, 1999	Feb 1, 1999	Feb 4, 1999	Additional Tables
BZ Amendment 009	Feb 12, 1999	Feb 16, 1999	Feb 22, 1999	Noted NAI. Additional information on Bulk drug batches
C Amendment 010	Feb 25, 1999	Feb 26, 1999	Mar 8, 1999	Noted NIA. DMF
BC Amendment 012	Mar 11, 1999	Mar 12, 1999	Mar 16, 1999	Revised stability data
BC Amendment 013	Mar 12, 1999	Mar 15, 1999	Mar 29, 1999	Corrected electronic files. Replaces some files of amendment 006.
BZ Amendment 018	May 5, 1999	May 6, 1999	May 7, 1999	CRC issues
BC Amendment 019	May 19, 1999	May 20, 1999	Jun 01, 1999	Copy of the CPSC Response
BC Amendment 020	May 27, 1999	May 27, 1999	Jun 4, 1999	Implementation of CPSC
BC Amendment 022	Jun 6, 1999	Jul 7, 1999	Jul 13, 1999	Information for T-con.
BL Amendment 023	Aug 6, 1999	Aug 9, 1999	Aug 16, 1999	Revised Label
BZ Amendment 025	Aug 20, 1999	Aug 23, 1999	Sep 9, 1999	IR response
C	Sep 8, 1999	Sep 14, 1999	Sep 22, 1999	Time frame agreement
BC Amendment 027	Oct 20, 1999	Oct 21, 1999	Oct 22, 1999	Labeling information

NAME & ADDRESS OF APPLICANT:
Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Rd./ P.O. Box 368
Ridgefield, CT 06877-0368

DRUG PRODUCT NAME:

Proprietary:	Aggrenox™ (Extended Release Capsules)
Nonproprietary/USAN:	Dipyridamole 200mg /Aspirin 25 mg
Code Name/#:	Dipyridamole: RA-8-BS
Chem.Type/Ther.Class:	Type P

PHARMACOLOGICAL CATEGORY: Combination anti-platelet agent intended for oral administration.

INDICATION:

DOSAGE FORM: Capsule
STRENGTH: 200 mg Dipyridamole / 25 mg Aspirin
ROUTE OF ADMINISTRATION: Oral
HOW DISPENSED: Rx

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:
Dipyridamole: 2,6-Bis-(diethanolamino)-4,8,-dipiperidinopyrimido-[5,4-d]-pyrimidine
Aspirin: Benzoic acid, 2-(acetyloxy)-salicylic acid acetate.

SUPPORTING DOCUMENTS:

DMF	Item	Holder	Status	Review	Letter

CONSULTS:
Establishment evaluations were requested in Jan 29, 1999 and Feb 2, 1999. Inspection were completed 3/16, 17, 18 ( ) 3/22-25, 1999 ( ), 3/29,30,31,1999 ( ).
Compliance final report is pending, 483 have been issued.
Request for a Trademark review was submitted Jan 26, 1999.

REMARKS/COMMENTS:
BC Amendment 027 presents the proposed revised carton label for the 60's count bottle which has the proposed statement concerning re dispensing the product from a non-compliant bottles to a compliant

CRC bottle. The immediate container and carton labeling for the proposed 10-count physician's sample are also provided.

The cartons contain an attached label with the following information:

[redacted]

CONCLUSIONS & RECOMMENDATIONS:

The attached label information is in agreement with the Consumer Product Safety Commission (CPSC) requirements concerning re-dispensing the product from a non-compliant bottle to a compliant CRC bottle (May 5, 1999 BZ Amendment).

The name provided in the carton samples is:

[redacted] The company is aware that it has to be corrected to:

[redacted]

The review of the new dissolution method by the Division of Clinical Pharmacology has concluded that the method is adequate.

An 18 months expiry date is recommended.
The Methods Validation package will be sent for verification.

From the standpoint of CMC this NDA may be approved.

/S/ 11/4/99
Maria Elena Ysem, MSc
Review Chemist, HFD-180

APPEARS THIS WAY
ON ORIGINAL

/S/ 11/4/99
Liang Zhou, PhD.
Acting Chemistry Team Leader, HFD-180

cc:
NDA 20-884
HFD-180/LTalarico
HFD-180/Div File/NDA 20-884
HFD-180/LZhou
HFD-180/MYsem
HFD-181/JDubeau
R/D Init by: LZhou
MY/ F/T 11-04-99/ c:\wordfiles\nda\20884911.4MY