CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020884

ADMINISTRATIVE/CORRESPONDENCE DOCUMENTS

DuBeau

NDA 20-884

MAY 20 1999

CHEMISTRY REVIEW – TEAM LEADER'S ADENDUM

DRUG PRODUCT: Aggrenox

SPONSOR: Boehringer Ingelheim Pharmaceuticals

ROUTE OF ADMINISTRATION: oral

DATE OF SUBMISSION: original – 12/15/98

REVIEWER: Ali Al-Hakim

REVIEW:

Labeling and Nomenclature consult dated May 14,1999 recommends that the drug product name (Aggrenox) is acceptable.

CONCLUSION

Acceptable.

APPEARS THIS WAY ON ORIGINAL

/S/ 5/20/1999

Ali Al-Hakim, PhD
Acting Chemistry Team Leader, HFD-180

APPEARS THIS WAY ON ORIGINAL

cc:
Div File
NDA 20-884
HFD-180/JDuBeau
HFD-180/AAlHakim
HFD-180/LTalarico
HFD-180/Gallo-Torres
HFD-180/EDuffy
N:\wordfiles\chem\nda20884tla.1ed

substantial evidence for prevention of stroke (vote: 10 yes; 0 no) but not for prevention of death (vote: 3 yes; 7 no). The Committee did not feel there were any particular safety concerns with the drug.

Reviewer's Conclusions and Recommendations:
The sponsor has demonstrated safety and effectiveness of Aggrenox (dipyridamole 200mg plus aspirin 25mg) given twice daily for preventing stroke in patients with recent ischemic stroke or TIA and I recommend that Aggrenox be approved for prevention of stroke in these patients.

Prior to approval outstanding chemistry, manufacturing and control issues and biopharmaceutics issues should be resolved.

With regard to the product labeling I recommend the following:

1. Though the dipyridamole/aspirin combination appeared to be more effective than aspirin in ESPS2, because the aspirin dose was so low (50mg daily) the study does not provide substantial evidence for superiority of the combination product over the entire range of aspirin doses (50-325mg) approved for treatment of stroke and TIA patients. Accordingly, in the labeling and in advertising claims superiority of Aggrenox to aspirin should be expressed as superior to "aspirin 50mg daily".

2. The labeling should reflect that for stroke or TIA patients who also have cardiovascular disease and for whom aspirin is indicated to prevent recurrent myocardial infarction or for angina pectoris, the aspirin in this product may not provide adequate treatment for the cardiac indications.

3. The labeling should indicate that there is no clear benefit of the dipyridamole/aspirin combination over aspirin with regard to safety.

4. Results of the clinical trial supporting the indication (ESPS2) should be summarized in the Clinical Trials section of the labeling. Also, even though this product is not being recommended for approval for prevention of death, because other treatment options for patients in whom Aggrenox are indicated for "prevention of stroke and death", the results obtained in ESPS2 for prevention of death should be displayed in the Clinical Trials section of the labeling for the information of practiotioners who will be choosing among available therapies.

5. The sponsor should rewrite the Warnings, Precautions and Adverse Events sections of the labeling to incorporate safety results from ESPS2 and from labeling and other experience with dipyridamole alone and aspirin alone.

6. The sponsor should update the Overdose section of the labeling.

/S/

Kathy M. Robie-Suh, M.D., Ph.D. 5/13/99

CSO/DuBeau

REQUEST FOR TRADEMARK REVIEW

To: Labeling and Nomenclature Committee
Attention: Dan Boring, Chair (HFD-530), 9201 Corporate Blvd. Room N461

From: Division of Gastrointestinal and Coagulation Drug Products		HFD-180
Attention: Julieann DuBeau 1/26/99		Phone: (301) 827-7310
Date: January 26, 1999		
Subject: Request for Assessment of a Trademark for a Proposed New Drug Product		
Proposed Trademark: Aggrenox		NDA/ANDA# 20-884
Established name, including dosage form: dipyridamole/aspirin Capsules		
Other trademarks by the same firm for companion products:		
Indications for Use (may be a summary if proposed statement is lengthy):		
Initial Comments from the submitter (concerns, observations, etc.): The PDUFA due date for this application is June 15, 1999.		

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

cc: Original 20-884; HFD-180/division file; HFD-180/DuBeau; HFD-180/Ysem

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 22, 1999

FROM: Lilia Talarico, M.D.; Director, Division of Gastrointestinal and Coagulation Drug Products, HFD-180 /S/ 11-22-99

SUBJECT: Approval Recommendation of Aggrenox™ for Patients who have had a Transient Ischemic Attack or Completed Stroke due to Thrombosis, NDA 20-884

TO: Florence Houn, M.D., M.P.H., F.A.C.P.; Director, Office of Drug Evaluation III, HFD-103

This memo summarizes the actions for NDA 20-884.

On December 15, 1998, Boehringer Ingelheim Pharmaceuticals, Inc. submitted NDA 20-884 for Aggrenox™ (aspirin/extended-release dipyridamole) Capsules to support the following indication [redacted]. On June 15, 1999, the Agency issued an approvable letter for the following revised indication: "to reduce the risk of stroke in patients who have had transient ischemia of the brain or completed stroke due to thrombosis".

The approval letter identified biopharmaceutical, pharmacology, and Chemistry, Manufacturing and Control (CMC) issues that required revision and additional information. Revisions to the proposed label were requested by the Agency.

Since June 15, 1999, the following issues have been satisfactorily resolved with sponsor:

I. Biopharmaceutics

A. Bioequivalence Issues: On October 26, 1999, the bioequivalence issues regarding the "to-be-marketed" Aggrenox™ and clinical trial formulations/batches used in ESPS2 (see Biopharmaceutics Review dated October 26, 1999).

B. Dissolution Analyses: On October 26, 1999, the dissolution analyses issues were resolved (see Biopharmaceutics Review dated October 26, 1999).

[redacted]

E. Population Pharmacokinetics Data from ESPS2: On November 3, 1999, Dr. Fossler's review suggested that the data in ESPS2 for subjects < 55 may not be sufficient to provide information on the adequacy of dose and made two recommendations.

II. Chemistry, Manufacturing and Controls: On August 6 and 20 and October 6, 1999 the sponsor submitted responses to the issues identified in the June 15, 1999 approvable letter. The responses were satisfactory (see Chemistry, Manufacturing and Controls Reviews dated October 13 and November 4, 1999).

III, Pharmacology Issues r/t Carcinogenicity: The sponsor's responses to the June 15, 1999, approvable letter were reviewed and found acceptable (see Pharmacology Review dated November 9, 1999).

IV. Labeling Issues:

Clinical: The endpoints in the Clinical Trials section were discussed with the firm by teleconference on November 18 and 19, 1999. The issues as discussed on November 19, 1999, were found to be acceptable (see attached November 19, 1999, facsimile).

NDA 20-884 is recommended for approval.

Attachment: November 19, 1999, facsimile

APPEARS THIS WAY
ON ORIGINAL

2 pages
REDACTED
Confidential
Commercial

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: May 13, 1999

From: Kathy M. Robie-Suh, M.D., Ph.D.
Medical Team Leader, HFD-180

Subject: NDA 20-884
Aggrenox (extended release dipyridamole 200mg/aspirin 25mg)
[submitted: December 15, 1998]

To: Director, Office of Drug Evaluation III (ODEIII)
Center for Drug Evaluation and Research, FDA

Through: Director, Division of Gastrointestinal and Coagulation Drug Products
(HFD-180) /S/ 5-13-99

The sponsor is seeking approval of Aggrenox, a fixed dose combination product consisting of extended release dipyridamole 200mg plus aspirin 25mg, given twice daily for use

Please refer also to my previous memorandum on this application dated April 14, 1999.

To support effectiveness of the drug product for the proposed indication the sponsor submitted report of ESPS2 (European Stroke Prevention Study 2), a multinational, randomized, double-blind, placebo-controlled trial. In that trial the combination of dipyridamole 200mg plus aspirin 25mg twice daily was shown to be more effective that either dipyridamole 200mg twice daily alone or aspirin 25mg twice daily alone in preventing subsequent stroke in patients who had suffered a completed ischemic stroke or TIA in the 3 months prior to starting study treatment. Both dipyridamole 200mg twice daily and aspirin 25mg twice daily were also superior to placebo for preventing stroke in the study. No benefit in reducing risk of either all cause mortality or death due to stroke was demonstrated for any of the treatments.

The safety profile of the combination product appears to be similar to that of the component drugs. Gastrointestinal adverse events (particularly diarrhea, nausea, and vomiting) and headache appeared to be associated with dipyridamole while bleeding events appeared to be associated more with aspirin use.

ESPS2 was presented and discussed in detail at the April 28, 1999 meeting of the Peripheral and Central Nervous System Advisory Committee. The Committee felt that the study provided

PATENT INFORMATION

The following is the patent information required to be submitted under 21 CFR 314.53:

(i)	Applicable Patent Numbers and Expiration Date of Each	There is no applicable patent at present. A patent application is, however, pending and this statement will be updated upon the issuance of a patent.
(ii)	Type of Patent	Not applicable
(iii)	Name of Patent Owner	Not applicable
(iv)	Entity authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 C.F.R §§ 314.52 and 314.95	Not applicable

By: David R. Brill

David R. Brill, Ph.D.

Title: Director, Drug Regulatory Affairs
Capacity: Applicant's Agent (Representative)

Date:

EXCLUSIVITY SUMMARY FOR NDA #: 20-884 SUPPL #_____

Trade Name: Aggrenox™ Generic Name: (aspirin/extended-release dipyridamole)

Applicant Name: Boehringer Ingelheim Pharmaceuticals, Inc. HFD #: 180

Approval Date If Known _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES/_X__/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /_X__/

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /_X__/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /_X_/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request? 3years

e) Has pediatric exclusivity been granted for this Active Moiety?

No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /___/ NO /_X_/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /_X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 12-836 Persantine (dipyridamole) Tablets

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X__/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X__/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /_X__/ NO /_ __/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /__/ NO /_X_/

If yes, explain: _____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /__/ NO /__/

If yes, explain: _____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

"European Stroke Prevention Study 2 (ESPS-2)"

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

APPEARS THIS WAY
ON ORIGINAL

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /_X__/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X__/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

___ European Stroke Prevention Study 2 (ESPS-2)

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ NO /___/ Explain:_____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /_X__/ Explain: See 12/15/98 original NDA submission volume 1.001. Study was not conducted under an IND.

NO /___/ Explain _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

APPEARS THIS WAY
ON ORIGINAL

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/

If yes, explain: _____

/S/ 11/18/99

Signature Date

Title: Regulatory Project Manager

/S/ 11-18-99

Signature of Office/ Division Director Date

APPEARS THIS WAY ON ORIGINAL

cc: Original NDA 20-884
HFD-180/Div. File
HFD-180/DuBeau
HFD-93 Mary Ann Holovac
R/d Init: Talarico 11/17/99
R/d Init: Collier 11/18/99
JD/November 16, 1999 (drafted)
JD/11/18/99/c:\mydocs\nda\20884911-exclusivity.doc

DUPLICATE

Boehringer Ingelheim

Lilia Talarico, M.D., Director
Division of Gastrointestinal and Coagulation Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room 6B-24
5600 Fishers Lane
Rockville, MD 20857

Boehringer Ingelheim
Pharmaceuticals Inc.

JUL 0 1 1999
HFD-180
EVALUATION AND RESEARCH

June 30,1999

AGGRENOX (extended release dipyridamole 200 mg/ aspirin 25 mg) Capsules:
NDA 20-884

David R. Brill, Ph.D.
Telephone 203-798-4340
Telefax 203-791-6262
E-Mail Dbrill@bi-pharm.com

900 Ridgebury Rd/P.O. Box 368
Ridgefield, CT 06877-0368
Telephone (203) 798-9988

Dear Dr. Talarico:

Reference is made to our New Drug Application (NDA 20-884) submitted for Aggrenox Capsules on December 15, 1998. Further reference is made to that NDA section 1.6 (Exclusivity Information: Volume 1.001, page 15) whereby pursuant to 21 CFR 314.108, market exclusivity is claimed for the Aggrenox drug product.

Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI) is hereby amending the subject NDA section 1.6 with additional information in support of the claimed market exclusivity. The submitted document certifies the level of financial support provided by BIPI for the ESPS-2 trial.

Please call me directly at the number provided if you have any questions or comments on this submission.

Sincere regards,

David R. Brill

David R. Brill, Ph.D.
Director, Drug Regulatory Affairs

KPMG

Marie-Curie-Straße 30
D-60439 Frankfurt am Main

Postfach 50 05 20
D-60394 Frankfurt am Main

Telefon (0 69) 95 87-0
Telefax (0 69) 95 87-10 50

Food and Drug Administration
Center of Drug Evaluation and Research
Document Control Room 6B-24
5600 Fishers Lane
Rockville, MD 20857

USA

June 16, 1999

Attn: Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation Drug Products

Re: AGGRENOX ™ Extended Release Capsules - NDA 20-884

Dear Dr. Talarico:

It is our understanding that Boehringer Ingelheim Pharmaceuticals, Inc. („BIPI") has submitted a New Drug Application to the United States Food and Drug Administration („FDA") on December 15, 1998 for a new pharmaceutical product, an extended release capsule containing 200 mg of dipyridamole and 25 mg of acetylsalicylic acid, identified in the NDA as AGGRENOX ™ Extended Release Capsules. The NDA number for the product is 20-884.

In support of BIPI's claim for exclusivity, the undersigned hereby certifies that it has examined the proofs of performance, including appropriate contracts and related invoices and is satisfied that BIPI has provided the cost of conducting the study essential for FDA approval, which study is identified as ESPS-2.

If any further information is required regarding the facts to which we are hereby certifying, please do not hesitate to contact us.

Respectfully submitted,

KPMG Deutsche Treuhand-Gesellschaft
Aktiengesellschaft
Wirtschaftsprüfungsgesellschaft

Horst-Jürgen Hadrys
Wirtschaftsprüfer

Heinrich Macke
Wirtschaftsprüfer

KPMG DEUTSCHE TREUHAND-GESELLSCHAFT AKTIENGESELLSCHAFT WIRTSCHAFTSPRÜFUNGSGESELLSCHAFT
WIRTSCHAFTS-PRÜFUNGS-GESELLSCHAFT
SIEGEL
BERLIN UND FRANKFURT a. M.

Aufsichtsratsvorsitzender:
WP Dipl.-Ing.
Christian Schnecke

Vorstand:
WP StB Dipl.-Kfm.
Axel Berger
WP StB RA
Dr. Bernd Erlo
WP RA StB
Dr. Wolfgang Fitzke
WP StB
Dr. Gerd Gelb

WP Dr. Martin Hoyos
RA StB
Dr. Heinrich Lüßmann
WP Dipl.-Kfm.
Ulrich Maas
WP StB
Dr. Ralf Nonnenmacher
WP StB Dipl.-Kfm.
Rüdiger Reinke
WP StB
Dr. Horst Schollein
WP Dipl.-Oec.
Bernd Ulrich Schmid

WP Dr. Wieland Schroff
WP StB
Prof. Dr. Klaus Stolberg
WP StB Dr. Peter Wiener
WP RA StB
Prof. Dr. Harald Wiedmann
Sprecher
WP StB Dipl.-Kfm.
Wolfgang Zielke
stellv. Sprecher

Zertifiziert nach
DIN EN ISO 9001

Sitz: Berlin und Frankfurt am Main

Handelsregister:
Charlottenburg (HRB 1077) und Frankfurt am Main (HRB 14348)

Bankverbindung:
Deutsche Bank AG, Frankfurt am Main, 983 866
BLZ 500 700 10

USt.-Mitr.: DE 136 791 84

KPMG Deutsche Treuhand-Gesellschaft
Aktiengesellschaft Wirtschaftsprüfungsgesellschaft
Mitglied von KPMG International

EXCLUSIVITY INFORMATION

1) The applicant, Boehringer Ingelheim Pharmaceuticals, Inc., believes that after approval of the New Drug Application, AGGRENOX™ Extended Release Capsules, the new drug that is the subject of this application and for which approval is sought, will be entitled to a period of marketing exclusivity under the provisions of 37 CFR 314.108, and is, therefore, claiming exclusivity.

2) Reference is made to 37 CFR 314.108(b)(4) to support the applicant's claim to exclusivity for AGGRENOX™ Extended Release Capsules.

3) The applicant claims exclusivity under 21 CFR 314.108(b)(4) and, pursuant to 21 CFR 314.50(j)(4), the following information is submitted to show that the application contains new clinical investigations that are essential to approval of the application and were conducted or sponsored by the applicant:

   (i) The undersigned hereby certifies that to the best of the applicant's knowledge each of the clinical investigations included in the application meets the definition of "new clinical investigation" set forth in 21 CRF 314.108(a).

   (ii) Attached hereto as Exhibit A is a list of all published studies or publically available reports of clinical investigations known to the applicant through a literature search that are relevant to the conditions for which the applicant is seeking approval. The undersigned hereby certifies that the applicant has thoroughly searched the scientific literature and, to the best of the applicant's knowledge, the list is complete and accurate and, in the applicant's opinion, such published studies or publically available reports do not provide a sufficient basis for the approval of the conditions for which the applicant is seeking approval without reference to the new clinical investigation(s) in the application. In the opinion of the applicant, such published studies or publically available reports do not provide a sufficient basis for the approval of the conditions for which the applicant is seeking approval without reference to the new clinical investigation(s) in the application

because they cannot and not serve as the primary source of evidence of effectiveness and safety of the new drug AGGRENOX® Capsules.

(iii) It is hereby certified that a predecessor in interest of the applicant provided substantial support for the clinical investigation that is essential to the approval of this application. More specifically, it is certified that the applicant, Boehringer Ingelheim Pharmaceuticals, Inc. is the U.S. marketing entity for the Boehringer companies. It is further certified that the clinical investigation known as the European Stroke Prevention Study-2 (ESPS-2) was conducted at several clinical centers outside of the United States, all of which were under contract with Boehringer Ingelheim International GmbH (BII), a Boehringer affiliate. Under such contracts, 100% of the cost of conducting ESPS-2 was paid by BII, and this fact will be verified by a certified statement of a certified public accountant, to be submitted under separate cover. The applicant is the U.S. marketing entity for the Boehringer companies and BII will, accordingly, convey to the applicant the exclusive right (including rights to results of ESPS-2) necessary to market AGGRENOX™ Extended Release Capsules in the U.S.

BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

By: David R. Brill

David R. Brill, Ph.D.

Title: Director, Drug Regulatory Affairs

Date:

CERTIFICATION REQUIREMENT

SECTION 306(k)(1) OF THE ACT
21 U.S.C. 355a(k)(1)

Boehringer Ingelheim Pharmaceuticals, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under subsection (a) or (b) [Section 306(a) or (b)], of the Federal Food, Drug and Cosmetic Act in connection with AGGRENOX™ (extended release dipyridamole 200 mg / aspirin 25 mg) Capsules.

Signature: Martin Kaplan

Name of Applicant: Martin Kaplan, M.D., J.D.
Vice-President, Drug Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals, Inc.

Date: May 27, 1999

Mailing Address Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877-0368

Memorandum

To: NDA 20-884

From: EDuffy/CMC TL /S/ 8/30/99

Date: 08/30/99

Re: Amendment Dated 8/20/99

Boehringer-Ingelheim, Inc. has submitted an amendment dated 8/20/99 in response to our approvable letter dated 6/15/99. From a CMC perspective, based upon the nature of the deficiency comments, and the firm's responses, this amendment is considered a class 2 re-submission.

The rationale for this determination is primarily due to the request for new dissolution data, based upon a new method that needed to be developed. The review of the amendment will require review of the new dissolution method and its validation, as well as of the comparative dissolution data comparing batches from ESPS 2 to the primary stability batches. Note that there were important manufacturing modifications made to the to-be-marketed product.

Other areas requiring CMC review include drug product manufacturing, regulatory specifications, stability, the container/closure system, and a DMF.

cc:
Div File NDA 20-884
HFD-180/JDuBeau
HFD-180/MYsern
HFD-180/EDuffy
HFD-180/LTalarico
HFD-180/SAurrechia
HFD-180/KRobie-Suh
HFD-180/AFarrell
HFD-103/FHoun
HFD-870/ASancho
HFD-870/DLee
N:\wordfiles/chem/nda/20-884type2.mem

CONFIDENTIAL

DuBeau

NDA 20-884

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: David R. Brill, Ph.D.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

AUG 26 1999

Dear Dr. Brill:

We acknowledge receipt on August 23, 1999, of your August 20, 1999, resubmission to your new drug application (NDA) for Aggrenox™ (aspirin and extended-release dipyridamole) Capsules.

This resubmission contains additional biopharmaceutical, chemistry, manufacturing, and controls (CMC), pharmacology, and labeling information submitted in response to our June 15, 1999. action letter.

We consider this a complete class 2 response to our action letter. Therefore, the user fee goal date is February 23, 2000.

If you have any questions, contact Julieann DuBeau, Regulatory Health Project Manager, at (301) 827-7310.

Sincerely,

/S/ 8-26-99

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Archival NDA 20-884
HFD-180/Div. Files
HFD-180/J.DuBeau
HFD-180/Duffy
HFD-180/Choudary
HFD-180/Robie-Suh
HFD-870/Lee

DuBEAU

NDA 20-884

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: David R. Brill, Ph.D.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

AUG 20 1999

Dear Dr. Brill:

Please refer to the meeting between representatives of your firm and FDA on August 3, 1999. A copy of our minutes of that meeting is enclosed. These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

If you have any questions, contact me at (301) 827-7310.

Sincerely,

/S/

Julieann DuBeau, RN, MSN
Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

cc:
Archival NDA 20-884
HFD-180/Div. Files
HFD-180/J.DuBeau
JD/August 20, 1999 (drafted)
JD/8/20/99/c:\mydocs\nda\20884908-minletter.doc

/S/8/20/99

GENERAL CORRESPONDENCE (MINUTES SENT)

MEMORANDUM OF MEETING MINUTES

Meeting Date: August 3, 1999
Time: 2:00 PM – 3:30 PM
Location: Parklawn Building, room 13B-45

Application: Aggrenox™ (aspirin and extended-release dipyridamole) Capsules

Type of Meeting: Type B: End of Review Conference

Meeting Chair: Dr. Lilia Talarico

Meeting Recorder: Ms. Julieann DuBeau

FDA Attendees, titles, and Office/Division:

Division of Gastrointestinal and Coagulation Drug Products (HFD-180)

Dr. L. Talarico; Division Director
Dr. S. Aurecchia; Deputy Division Director
Dr. E. Duffy; Chemistry Team Leader
Ms. J. DuBeau; Regulatory Health Project Manager

Division of Pharmaceutical Evaluation II (HFD-870)

Dr. M. Chen; Division Director
Mr. J. Hunt; Deputy Division Director
Dr. D. Lee; Biopharmaceutics Team Leader
Dr. A. Sancho; Biopharmaceutist

Office of Drug Evaluation III (HFD-103)

Dr. F. Houn; Office Director

External Constituent Attendees and titles:

Boehringer Ingelheim Pharmaceuticals, Inc.

Dr. M. Haehl; Sr. V.P. Medical and Regulatory Affairs
Dr. M. Kaplan; V.P. Drug Regulatory Affairs
Dr. D. Brill; Director, Drug Regulatory Affairs
Dr. M. Lamson; Senior Scientist, Pharmacokinetics
Dr. A. Ranhosky; Director, General Medicine
Ms. P. Watson; Director, Technical Regulatory Affairs

Boehringer Ingelheim Pharma KG Biberach

Dr. P. Boehm; CMC and Preclinical Project Manager
Dr. U. Brauns; Pharmaceutics
Dr. R. Brickl; Pharmacokinetics
Dr. G. Duschler; Analytics

APPEARS THIS WAY
ON ORIGINAL

Background:

Boehringer Ingelheim Pharmaceuticals, Inc. submitted NDA 20-884 on December 15, 1998, with the following proposed indication: On May 26, 1999, the firm received a CMC information request letter. On June 15, 1999, the firm received an Approvable action letter which referred to the May 26, 1999, letter and contained biopharmaceutics, pharmacology/toxicology, and labeling issues for the following indication: "To reduce the risk of stroke in patients who have had transient ischemia of the brain or completed ischemic stroke due to thrombosis." The firm requested this meeting to further discuss items IC and ID in the June 15, 1999, letter (see Attachment #1).

Meeting Objective:

To reach an agreement with the Agency that items IC (food effect) and ID (extended-release claim) in the June 15, 1999, Approvable action letter are designated as Phase IV commitments as opposed to pre-approval requirements.

Discussion:

Dr. Houn began the discussion by requesting an update regarding the firm's responses to items IA (linkage) and IB (dissolution) in the June 15, 1999, letter followed by a presentation of items IC (food effect) and ID (extended-release claim). Items IA-ID (bolded type) are reiterated below followed by the discussion.

Item IA:

Bioequivalence issue between the to-be-marketed Aggrenox™ Capsules and all clinical trial formulations/batches:

The to-be-marketed formulation of Aggrenox™ Capsules was not used in the pivotal clinical trial ESPS-2. Instead, eight different "formulations/batches" of Aggrenox™ Capsules were used in this trial, for which only one of these "formulations/batches" was tested for bioequivalence with the to-be-marketed formulation (i.e., in bioequivalence Study #IP 9.123).

The firm stated that they are prepared to fully respond to this action item on August 20, 1999. They referred to a submission dated February 12, 1999, in which they describe and link together the following information: bulk drug batches (both substance and product), different formulations, and where they were used/tested in stability, clinical trials, and biopharmaceutics studies. In addition, the firm referred to a submission dated June 30, 1999, in which they highlight information found in the original NDA application and the February 12, 1999, submission that address this issue. The Division stated that the information referred to appears to be an appropriate response to item IA, however, it will need to be reviewed in full.

Item IB:

Dissolution analyses:

Item IC:

Food effect:

Please conduct a food effect study to evaluate the effect of food/meals on the absorption of dipyridamole and aspirin, and to assess the potential for "dose-dumping" of the extended release dipyridamole pellets of the to-be-marketed Aggrenox™ Capsules.

The firm stated that there is no drug-drug interaction between aspirin and dipyridamole extended release as evidenced by the interaction Study 9.69 (U89-0187) and the ESPS-2 study, in which patients in the latter study received Aggrenox without respect to food intake. Dr. Chen stated that the firm's claim of lack of drug-drug interaction is unsubstantiated based on the results of Study 9.69 (U89-0187). The firm stated that dipyridamole extended-release has been marketed in a number of countries since 1983 (dosed without respect to food intake) without major safety issues. Dr. Lee stated that there is no reference product approved in the United States (i.e. extended-release dipyridamole) to compare to Aggrenox™. The firm stated that neither the single dose food study (U92-0034) nor the steady state study (U85-0619) detected a relevant food effect and therefore the potential for dose dumping is low.

After much discussion and consideration of the above points, it was agreed that the firm would submit a proposed food effect study protocol for Aggrenox™ for review by the biopharmaceutics team. The firm should commit in writing to conducting the food effect study (based on a mutually agreed upon protocol) as Phase IV. The written commitment would include a timeframe of when the study report would be submitted to the NDA.

Item ID:

Extended release claim:

Provide information/data comparing the dipyridamole pharmacokinetics obtained in subjects receiving i) the to-be-marketed Aggrenox™ Capsule and ii) the FDA approved immediate

release dipyridamole formulation given concurrently with the aspirin tablet that is included in the Aggrenox™ Capsule to substantiate the extended release claim for the dipyridamole pellet component.

Dr. Chen stated that the information submitted to the NDA at present is not adequate to substantiate an extended-release claim. It was agreed that the firm would commit in writing to conduct a pharmacokinetic study as Phase IV comparing subjects receiving the to-be-marketed Aggrenox™ and the FDA approved immediate release dipyridamole formulation given concurrently with the aspirin tablet that is included in the Aggrenox™ Capsule to substantiate the extended release claim for the dipyridamole pellet component. The written commitment would include a timeframe of when the study report would be submitted to the NDA. The firm stated that a protocol for this proposed study would be submitted in approximately 4-5 weeks.

General Discussion:

After discussion of items IA-ID, the firm stated that they plan to fully respond to the June 15, 1999, Approvable letter on August 20, 1999. Determination of a complete response will be made within one week of submission. If the response is complete, the class of resubmission (i.e. Type 1 or Type 2) will be determined. Labeling negotiations will occur in the next review cycle (after receipt of a complete response to the June 15, 1999, letter).

Minutes Prepared: /S/ 8/20/99

Chair Concurrence: /S/ 8-20-99

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELECON

DuBEAU

DATE: August 20, 1999

APPLICATION NUMBER: NDA 20-884; Aggrenox™
(aspirin and extended-release dipyridamole) Capsules

BETWEEN:

Name: Dr. David Brill; Director, Drug Regulatory Affairs
Dr. Rolf Brickl; Pharmacokinetics
Dr. Martin Kaplan; V.P., Drug Regulatory Affairs

Phone: (203) 798-4340

Representing: Boehringer Ingelheim Pharmaceuticals, Inc.

AND

Name: Ms. Julieann DuBeau; Regulatory Health Project Manager
Dr. David Lee; Biopharmaceutics Team Leader
Dr. Ronald Kavanagh; Clinical Pharmacology & Biopharmaceutics
Dr. Mei-Ling Chen; Division Director of DPE II
Mr. John Hunt; Deputy Division Director of DPE II
Dr. Lilia Talarico; Division Director

Division of Gastrointestinal and Coagulation Drug Products. HFD-180

SUBJECT: Discussion of Firm's Proposed Food Effect Protocol

BACKGROUND:

Boehringer Ingelheim Pharmaceuticals, Inc. submitted NDA 20-884 on December 15, 1998, with the following proposed indication:

May 26, 1999, the firm received a CMC information request letter. On June 15, 1999, the firm received an Approvable action letter which referred to the May 26, 1999, letter and contained biopharmaceutics, pharmacology/toxicology, and labeling issues for the following indication: "To reduce the risk of stroke in patients who have had transient ischemia of the brain or completed ischemic stroke due to thrombosis." On August 3, 1999, a meeting was held with the firm to discuss, among other issues, item IC of the June 15, 1999, action letter. Item IC is reiterated as follows: "Please conduct a food effect study to evaluate the effect of food/meals on the absorption of dipyridamole and aspirin, and to assess the potential for 'dose dumping' of the extended release dipyridamole pellets of the to-be-marketed Aggrenox™ Capsules." In this

meeting it was agreed that the firm would submit a proposed food effect study protocol for Aggrenox™ for review by the biopharmaceutics team. In addition, the firm would commit in writing to conducting the food effect study (based on a mutually agreed upon protocol) as Phase IV. The written commitment would include a timeframe of when the study report would be submitted to the NDA. This teleconference was scheduled to provide feedback regarding the firm's proposed food effect protocol submitted August 11, 1999, received August 12, 1999.

TODAY'S PHONE CALL:

Dr. Chen stated the proposed protocol (a multi-dose food effect study) included too much variability to provide the information needed from a regulatory perspective. She suggested that a single-dose food effect study would be sufficient in terms of regulatory requirements. The firm stated that they wanted to perform the multi-dose study to provide information beyond the required regulatory information. Dr. Kavanaugh stated that if the firm wished to proceed with the currently proposed protocol, the protocol must be amended as follows:

1. The blood sampling on day 1 should be increased to provide for a complete profile. The sampling scheduled should be the same as that defined for the last day of the study.

2. In the fasted arm of the study, the delay in administration of drug should be extended from the current 1 hour to at least a 2 hour delay on day 1.

3. A precise definition of both the continental breakfast and dinner should be provided in terms of describing their fat and caloric content.

The firm committed to revising the currently proposed protocol as stated above. In addition. the firm agreed to provide the full study report to the NDA within 6 months from the date of this teleconference.

The call was then concluded.

FOLLOW-UP:

The firm submitted a complete response to the June 15, 1999, Approvable action letter on August 20, 1999, (received August 23, 1999). In the firm's resubmission, they committed in writing to conduct a food effect study (with revisions as stated above) as Phase IV and provide the full study report within 6 months from August 20, 1999.

/S/ 9/14/99
Julieann DuBeau, RN, MSN
Regulatory Health Project Manager

DuBeau

NDA 20-884

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: David R. Brill, Ph.D.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

JUL 27 1999

Dear Dr. Brill:

Please refer to the teleconference between representatives of your firm and FDA on July 1, 1999.

A copy of our minutes of that teleconference is enclosed. These minutes are the official minutes of the teleconference. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

If you have any questions, contact me at (301) 827-7310.

Sincerely,

Julieann DuBeau, RN, MSN
Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

cc:
Archival NDA 20-884
HFD-180/Div. Files
HFD-180/J.DuBeau
JD/July 27, 1999 (drafted)
JD/7/27/99/c:\mydocs\nda\20884907-minletter.doc

/S/ 7/27/99

GENERAL CORRESPONDENCE (MINUTES SENT)

MEMORANDUM OF TELECON

DATE: July 1, 1999

APPLICATION NUMBER: NDA 20-884; Aggrenox™ (dipyridamole/aspirin) Capsules

BETWEEN:

Name: Dr. David Brill; Director, Drug Regulatory Affairs
Dr. Peter Boehm; CMC and Preclinical Project Manager
Dr. Rolf Brickl; Pharmacokinetics
Dr. Gerold Duschler; Analytics
Dr. Scott McGraw; CMC Administrator
Ms. Eileen Wyka; Technical Regulatory Affairs

Phone: (203) 798-4340

Representing: Boehringer Ingelheim Pharmaceuticals, Inc.

AND

Name: Ms. Julieann DuBeau; Regulatory Health Project Manager
Dr. Eric Duffy; Chemistry Team Leader
Ms. Maria Ysern; Chemist
Dr. David Lee; Biopharmaceutics Team Leader
Dr. Alfredo Sancho; Biopharmaceutist

Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Clarification of May 26, 1999, CMC information request letter and June 15, 1999, Approvable action letter

BACKGROUND:

Boehringer Ingelheim Pharmaceuticals, Inc. submitted NDA 20-884 on December 15, 1998, with the following proposed indication: [redacted] On May 26, 1999, the firm received a CMC information request letter. On June 15, 1999, the firm received an Approvable action letter which referred to the May 26, 1999, letter and contained biopharmaceutics, pharmacology/toxicology, and labeling issues for the following indication: "To reduce the risk of stroke in patients who have had transient ischemia of the brain or completed ischemic stroke due to thrombosis." The firm requested this teleconference to obtain clarification of item B1 in the May 26, 1999, letter and items IA and IB in the June 15, 1999, letter (see attached letters).

TODAY'S PHONE CALL:

Regarding items B1 in the May 26, 1999, CMC letter, and IB in the June 15, 1999, action letter, the firm stated that

Dr. Duffy stated that the Division has received the firm's June 30, 1999, facsimile (hard copy submitted 6/30/99, received 7/2/99) in preparation for today's teleconference. He stated that based on his cursory review of the document, the firm has not adequately addressed item B1 in the May 26, 1999, letter.

Regarding items IA in the June 15, 1999, action letter, the firm stated that a significant amount of this information has been previously submitted within the original application dated December 15, 1998, and in an amendment dated February 12, 1999. The firm stated that no reformulation of Aggrenox™ has occurred over time. Dr. Lee stated that the firm needs to address item IA as stated in the June 15, 1999, action letter with whatever further information is available.

The call was then concluded.

/S/ 7/27/99
Julieann DuBeau, RN, MSN
Regulatory Health Project Manager

Attachments (2)

Concur: Eric P. Duffy 7/27/99

DuBeau

NDA 20-884

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: David R. Brill, Ph.D.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

MAY 26 1999

Dear Dr. Brill:

Please refer to your pending December 15, 1998, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aggrenox™ (dipyridamole/aspirin) Capsules.

We also refer to your submissions dated January 13, 14, 18, 26, 29, February 12, 25, March 11, 12, and May 5, 1999.

We have completed our review of the Chemistry, Manufacturing, and Controls (CMC) section of your submission and have the following information requests:

A. Drug Product manufacture:

1. With respect to the [redacted] please provide information regarding [redacted] when the [redacted]

2. Regarding the [redacted] in your December 15, 1998, submission you indicate that an [redacted] are met. Since product has been [redacted] the Master Batch Record should be [redacted] In addition, provide justification for [redacted]

3. Regarding the [redacted] please clarify the statement made in Section 4.3.5.2.1.1. of your December 15, 1998, submission (volume 1.005, page 11) that the [redacted]

4. Regarding [redacted] please provide:

   a. a description of the [redacted] test method(s).
   b. data from [redacted] testing [redacted]

c. sample calculations from the
d. results of the testing from the

5. To achieve the required dipyridamole
Please justify the need

6. Concerning the preparation of the Aggrenox™ Extended Release Capsules, please explain why there seems to be a

7. The dipyridamole in some cases. Please indicate whether this is the If a is used, describe the qualification criteria.

8. Please indicate the used, at what , and under what conditions the during the preparation of the used in the manufacturing of the

9. During the preparation of the , please indicate the used to

10. Specify for manufacturing process, and provide data to justify the proposed

B. Drug Product Specifications:

1. The proposed dissolution method calls for testing While independent testing of each active component is acceptable, a method must be established in which the is tested. Provide dissolution data using the revised method for the pivotal clinical, pivotal PK, and primary stability batch(es).

2. Although the results of the for the capsules give values mostly you have proposed a specification Please provide a revised specification that more closely reflects test data.

3. Please be aware that only one set of regulatory specifications is permitted. If tighter release specifications are needed, these should be in-house specifications. Revise the proposed regulatory specifications accordingly.

C. Container/Closure System:

1. Please establish an acceptance test for [redacted] since [redacted] is a critical parameter that can affect product stability.

2. The indicator test [redacted] used for [redacted] packaging system should be validated, and results of the validation should be submitted.

D. Stability:

1. The stability testing for [redacted] was stated to have been done at [redacted] Provide data that indicate the actual conditions employed.

2. Please explain why the testing points do not include the 0, 3, and 6 month time periods.

3. Provide all new stability data available to date. In addition, provide dissolution data using the current method as well as the new method for testing the intact capsule.

4. The proposed expiry date will be determined after the dissolution testing method issue is resolved. Please note that the expiry dating period should be based upon first introduction of the active ingredient.

E. Environmental Assessment:

State the amount of drug substance projected to be manufactured based on marketing estimates for maximum yearly production of the drug product, and calculate the amount per day entering the aquatic environment. This would allow us to corroborate the Environmental Introduction Concentration at the point of entry, and verify that it is [redacted] [redacted] Please refer to the Federal Register Notice dated July 29, 1997, and the Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements.

F. Drug Master Files (DMF)

The following DMFs related to this application have been reviewed and found deficient:

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If you have any questions, contact Julieann DuBeau, Regulatory Health Project Manager, at (301) 827-7310.

Sincerely,

/S/ 5/26/99

Eric P. Duffy, Ph.D.
Chemistry Team Leader for the
Division of Gastrointestinal and Coagulation Drug Products, (HFD-180)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

cc:
Archival NDA 20-884
HFD-180/Div. Files
HFD-180/J.DuBeau
HFD-180/Duffy
HFD-180/Ysem
HFD-820/DNDC Division Director (only for CMC related issues)

NDA 20-884

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: David R. Brill, Ph.D.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

JUN - 4 1999

Dear Dr. Brill:

Please refer to your pending December 15, 1998, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aggrenox™ (dipyridamole/aspirin) Capsules which includes study reports of your 105-week oral carcinogenicity study in mice (U79-0257) and 125-week oral carcinogenicity study in rats (U79-0258).

We have completed our review of your submission and consulted the Center's Executive Carcinogenicity Assessment Committee, and have the following information requests:

1. Clarify how the conduct of the mouse and rat carcinogenicity studies deviated from GLP regulations, and the significance of these deviations.

2. Perform a statistical analysis on the incidence of thymoma in the 125-week oral carcinogenicity study in rats to determine its significance.

3. Provide the historical control data of the tumor incidence in Chbb:THOM rats in the testing laboratory during 1974-1979.

4. Submit available data from the literature on aspirin plasma clearance in mice and humans.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If you have any questions, contact Julieann DuBeau, Regulatory Health Project Manager, at (301) 827-7310.

Sincerely,

APPEARS THIS WAY
ON ORIGINAL

Kati Johnson
Supervisory Consumer Safety Officer
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Archival NDA 20-884
HFD-180/Div. Files
HFD-180/J.DuBeau
HFD-180/Choudary
DISTRICT OFFICE
R/d Init: Choudary 5/27/99
R/d Init: Johnson 6/3/99
JD/May 27, 1999 (drafted)
JD/6/4/99/c:\mydocs\nda\20884905-CAC-IR-ltr.doc

/S/ 6/4/99

APPEARS THIS WAY
ON ORIGINAL

INFORMATION REQUEST (IR)

CSO|Division

MEMORANDUM OF TELECON

DATE: April 13, 1999

APPLICATION NUMBER: NDA 20-884; Aggrenox™ (dipyridamole/aspirin) Capsules

BETWEEN:

Name: Dr. David Brill; Director, Drug Regulatory Affairs
Dr. James Street; Aggrenox team Statistician

Phone: (203) 798-4340

Representing: Boehringer Ingelheim Pharmaceuticals, Inc.

AND

Name: Ms. Julieann DuBeau; Regulatory Health Project Manager
Dr. Kathy Robie-Suh; Hematology Team Leader
Dr. Mohamed Al-Osh; Acting Statistical Team Leader
Dr. Mushfiqur Rashid: Statistician

Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Request for Statistical Information Regarding Pending NDA

BACKGROUND:

Boehringer Ingelheim Pharmaceuticals, Inc. submitted NDA 20-884 on December 15, 1998, with the following proposed indication: [redacted] Dr. Al-Osh requested that the firm provide references, if available, relating to the interim analysis performed during the ESPS-2 Phase III pivotal trial. (See attached fax dated April 6, 1999). Dr. Al-Osh requested that the firm be contacted to request additional information to assist with the statistical review of the pending Aggrenox NDA.

TODAY'S PHONE CALL:

Dr. Al-Osh requested that the firm submit the following information to the NDA:

1. Interim analysis results and how they were used to increase the sample size,
2. Meeting minutes from the steering committee regarding the increase in sample size,
3. Interim reports,
4. Clear copy of the statistical methodology included in the study protocol,
5. Primary endpoint clarification,

6. Detailed description of the randomization process, and
7. Detailed results of Center 2013, which was excluded from the statistical analysis.

Dr. Brill stated that he would submit the above requested information this week. The call was then concluded.

APPEARS THIS WAY
ON ORIGINAL

/S/ 4/19/99
Julieann DuBeau, RN, MSN
Regulatory Health Project Manager

cc: Original NDA 20-884
HFD-180/Div. File
HFD-180/DuBeau
HFD-180/Al-Osh
HFD-180/Rashid
R/d Init: Al-Osh 4/19/99
JD/April 15, 1999 (drafted)
JD/4/19/99/c:\mydocs\nda\20884904-tcon-stat.doc

APPEARS THIS WAY
ON ORIGINAL

TELECON

CSDoC

MEMORANDUM OF TELECON

DATE: March 8, 1999

APPLICATION NUMBER: NDA 20-884; Aggrenox™ (dipyridamole/aspirin) Capsules

BETWEEN:

Name: Dr. David Brill; Director, Drug Regulatory Affairs
Dr. Alan Ranhosky: Aggrenox team Medical Monitor
Dr. James Street; Aggrenox team Statistician
Dr. Martin Kaplan; Vice President Drug Regulatory Affairs

Phone: (203) 798-4340

Representing: Boehringer Ingelheim Pharmaceuticals, Inc.

AND

Name: Ms. Julieann DuBeau; Regulatory Health Project Manager
Dr. Lilia Talarico; Division Director
Dr. Kathy Robie-Suh; Hematology Team Leader
Dr. Ann Farrell; Medical Officer

Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Discussion of the Proposed Background Information Package for the Peripheral and Central Nervous System Drugs Advisory Committee (PCNS) Meeting

BACKGROUND:

Boehringer Ingelheim Pharmaceuticals, Inc. submitted NDA 20-884 on December 15, 1998, with the following proposed indication: The application will be presented at the PCNS Drugs Advisory Committee Meeting on April 28, 1999. The firm requested this teleconference to discuss the application issues that should be addressed and included in the background information package that will be distributed to the Agency and PCNS committee members.

TODAY'S PHONE CALL:

Dr. Talarico began the conversation by stating that the firm's application will be discussed at the April 28, 1999, PCNS Drugs Advisory Committee Meeting, and the panel will include members from the Cardio-Renal Drugs Advisory Committee. Dr. Talarico suggested that the firm focus

on the following issues:

1. Fixed Combination Efficacy: The firm must demonstrate that each component (i.e., aspirin and dipyridamole) is effective compared to placebo, and that the combination is more effective than each component (particularly aspirin).

2. Fixed Combination Safety: The firm must demonstrate that each component is safe, and that the combination does not increase risk.

3. Dosage of aspirin and dipyridamole: The firm must justify the dosage of aspirin and dipyridamole.

4. Robustness of a Single Trial: The firm must address the robustness of a single pivotal trial by following the Agency's guidance entitled "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products" (Issued 5/14/98, Posted 5/14/98).

The firm was informed that Ms. Sandra Titus, Executive Secretary of the PCNS Drugs Advisory Committees, will provide them as well as committee members with the Agency's medical and statistical reviews at least two weeks prior to the scheduled meeting. The proposed questions for the advisory committee members' consideration will be faxed to the firm as soon as they are available. Dr. Talarico encouraged the firm to submit their draft background information package for comment. The call was then concluded.

/S/ 3/12/99

APPEARS THIS WAY
ON ORIGINAL

Julieann DuBeau, RN, MSN
Regulatory Health Project Manager

APPEARS THIS WAY
ON ORIGINAL

cc: Original NDA 20-884
HFD-180/Div. File
HFD-180/DuBeau
HFD-180/Robie-Suh
HFD-180/Farrell
R/d Init: Talarico 3/11/99
JD/March 11, 1999 (drafted)
JD/3/12/99/c:\mydocs\nda\20884903-tcon-PCNS.doc

TELECON

CSO Eu Pen

MEMORANDUM OF TELECON

DATE: March 1, 1999

APPLICATION NUMBER: NDA 20-884; Aggrenox™ (dipyridamole/aspirin) Capsules

BETWEEN:

Name: Dr. David Brill; Director, Drug Regulatory Affairs
Dr. James Street; Senior Statistician
Phone: (203) 798-4340
Representing: Boehringer Ingelheim Pharmaceuticals, Inc.

AND

Name: Ms. Julieann DuBeau; Regulatory Health Project Manager
Dr. Lilia Talarico; Division Director
Dr. Kathy Robie-Suh; Medical Officer
Dr. Ann Farrell; Medical Officer
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Discussion of the February 23, 1999, Medical Information Request Letter

BACKGROUND:

Boehringer Ingelheim Pharmaceuticals, Inc. submitted NDA 20-884 on December 15, 1998. Contained in the NDA submission is the original ESPS-2 (pivotal trial) study report and an "efficacy database" created by the firm. A medical information request letter was sent to the firm on February 23, 1999 (attached). The firm requested clarification of the referenced letter.

TODAY'S PHONE CALL:

Dr. Brill was called and informed that the requested missing information in the ESPS-2 study report as outlined in the February 23, 1999, Division letter refers specifically to the ESPS-2 database, not the "efficacy database" created by the firm. Dr. Talarico referred the firm to the August 26, 1997, meeting minutes in which she requested FULL study reports. Dr. Robie-Suh stated that the firm should provide a connection between the ESPS-2 study report and the "efficacy database" created by the firm regarding any differences in subgroups, clinical endpoints, etc. Dr. Farrell stated that she is reviewing both the ESPS-2 study report and the "efficacy database" in their entireties. The call was then concluded.

/S/ 3/9/99
Julieann DuBeau, RN, MSN
Regulatory Health Project Manager

NDA 20-884

Boehringer Ingelheim
Attention: David R. Brill, Ph.D.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

FEB 23 1999

Dear Dr. Brill:

Please refer to your pending December 15, 1999 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aggrenox™ (dipyridamole/aspirin) Capsules.

We are reviewing the clinical section of your submission and request that you perform the following subgroup analyses and submit a revised printout of the cited tables:

I. Stroke

A. Non-fatal stroke (see Table 9.3.3:1, volume 116, pages 105-106)

1. Ischemic Heart Disease (yes or no)
2. MI history
3. Diabetes (yes or no)
4. IDDM/NIDDM
5. Hypertension (yes or no)
6. Diastolic BP (<90 mm Hg or ≥ 90 mm Hg)
7. Systolic BP (<160 mm Hg or ≥ 160 mm Hg)

B. Fatal-on-first stroke (see Table 9.3.3:2, volume 116, pages 107-108)

1. Ischemic Heart Disease (yes or no)
2. MI history
3. Diabetes (yes or no)
4. IDDM/NIDDM
5. Hypertension (yes or no)
6. Diastolic BP (<90 mm Hg or ≥ 90 mm Hg)
7. Systolic BP (<160 mm Hg or ≥ 160 mm Hg)

C. Fatal-only stroke (see Table 9.3.3:3, volume 116, pages 109-110)

1. Ischemic Heart Disease (yes or no)
2. MI history
3. Diabetes (yes or no)
4. IDDM/NIDDM
5. Hypertension (yes or no)
6. Diastolic BP (<90 mm Hg or ≥ 90 mm Hg)
7. Systolic BP (<160 mm Hg or ≥ 160 mm Hg)

II. Myocardial Infarction

A. Myocardial infarction (see Table 9.3.3:6, volume 116, page 113)

1. CTS-NMR Normal, Abnormal, and Confirming
2. Imaging Normal, Abnormal, and Confirming
3. Previous CVA anytime, ≥ 1 year, < 1 year, and none
4. Cerebral Location Hemispheric, Brainstem, Right, Left, and Uncertain
5. Diabetes (yes or no)
6. IDDM/NIDDM

B. Non-fatal myocardial infarction (see Table 9.3.3:7, volume 116, page 114)

1. CTS-NMR Normal, Abnormal, and Confirming
2. Imaging Normal, Abnormal, and Confirming
3. Previous CVA anytime, ≥ 1 year, < 1 year, and none
4. Cerebral Location Hemispheric, Brainstem, Right, Left, and Uncertain
5. Diabetes (yes or no)
6. IDDM/NIDDM
7. Age < 60 years and ≥ 60 years
8. Hypertension (yes or no)
9. Diastolic BP (<90 mm Hg or ≥ 90 mm Hg)
10. Systolic BP (<160 mm Hg or ≥ 160 mm Hg)

C. Fatal myocardial infarction (see Table 9.3.3:8, volume 116, page 115)

1. CTS-NMR Normal, Abnormal, and Confirming
2. Imaging Normal, Abnormal, and Confirming
3. Previous CVA anytime, ≥ 1 year, < 1 year, and none
4. Cerebral Location Hemispheric, Brainstem, Right, Left, and Uncertain
5. Diabetes (yes or no)
6. IDDM/NIDDM
7. Age < 60 years and ≥ 60 years
8. Hypertension (yes or no)

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9. Diastolic BP (<90 mm Hg or ≥ 90 mm Hg)
10. Systolic BP (<160 mm Hg or ≥ 160 mm Hg)

III. Ischemic events

A. Ischemic events (see Table 9.3.3:9, volume 116, page 116)

Bamford (classification): TACI, PACI, LACI, and POCI

B. Non-fatal ischemic events (see Table 9.3.3:10, volume 116, page 117)

1. CTS-NMR Normal, Abnormal, and Confirming
2. Imaging Normal, Abnormal, and Confirming
3. Previous CVA anytime, ≥ 1 year, < 1 year, and none
4. Cerebral Location Hemispheric, Brainstem, Right, Left, and Uncertain
5. Bamford (classification): TACI, PACI, LACI, and POCI

C. Fatal ischemic events (see Table 9.3.3:11, volume 116, page 118)

1. CTS-NMR Normal, Abnormal, and Confirming
2. Imaging Normal, Abnormal, and Confirming
3. Previous CVA anytime, ≥ 1 year, < 1 year, and none
4. Cerebral Location Hemispheric, Brainstem, Right, Left, and Uncertain
5. Bamford (classification): TACI, PACI, LACI, and POCI

D. Other vascular events (see Table 9.3.3:12, volume 116, page 119)

1. CTS-NMR Normal, Abnormal, and Confirming
2. Imaging Normal, Abnormal, and Confirming
3. Previous CVA anytime, ≥ 1 year, < 1 year, and none
4. Cerebral Location Hemispheric, Brainstem, Right, Left, and Uncertain

In addition to the above subgroup analyses, we request the following:

1. Locate in the NDA or provide the liver function test results and analyses as specified in the original ESPS-2 protocol.

2. In the study report for ESPS-2, you state that carotid endarterectomies will be listed in serious adverse events. However, the table in volume 116, page 147, does not list carotid endarterectomies as a category. Submit this information or provide a reference as to where it can be located in the NDA.

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We would appreciate your prompt written response so we can continue our evaluation of your NDA.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If you have any questions, contact Julieann DuBeau, Regulatory Health Project Manager at (301) 827-7310.

Sincerely,

/S/ 2/23/99

Kati Johnson
Supervisory Consumer Safety Officer
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

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cc:
Archival NDA 20-884
HFD-180/Div. Files
HFD-180/J.DuBeau
HFD-180/Farrell
HFD-180/Talarico
DISTRICT OFFICE
R/d Init: Johnson 2/22/99
R/d Init: Farrell 2/22/99
JD/February 19, 1999 (drafted)
JD/2/23/99/c:\mydocs nda\20884902-advletter.doc

/S/ 2/23/99

APPEARS THIS WAY
ON ORIGINAL

INFORMATION REQUEST (IR)

CSO/DuBeau

MEMORANDUM OF TELECON

DATE: February 9, 1999

APPLICATION NUMBER: NDA 20-884; Aggrenox™ (dipyridamole/aspirin) Capsules

BETWEEN:

Name: Dr. David Brill; Director, Drug Regulatory Affairs
Phone: (203) 798-4340
Representing: Boehringer Ingelheim Pharmaceuticals, Inc.

AND

Name: Ms. Julieann DuBeau; Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Request for Additional Information

BACKGROUND:

Boehringer Ingelheim Pharmaceuticals. Inc. submitted NDA 20-884 on December 15, 1998. After the February 2, 1999, filing meeting, the firm was contacted and requested to provide additional information.

TODAY'S PHONE CALL:

Dr. Brill was called and requested to provide the information listed below regarding NDA 20-884.

1. A table to include which bulk drug batches and specific formulations were used in which studies (including stability, clinical, and biopharmaceutics studies).

2. The status of the waiver request for the child-resistant closure from the Consumer Product Safety Commission.

3. Raw data from the pivotal bioequivalence studies in Excel or ASCII on Compact Disk.

4. The content of the meals, snacks, and beverages (including water) provided in the food-effect studies (#IP Belg 84 and #IP Jap Food) as well as the time in which each patient received the study drug in relation to meals, snacks, and beverages. In addition, the composition of the food with respect to kcal, protein, fat, and carbohydrates.

The call was then concluded.

APPEARS THIS WAY
ON ORIGINAL

/S/ 2/11/99

Julieann DuBeau, RN, MSN
Regulatory Health Project Manager

cc: Original NDA 20-884
HFD-180/Div. File
HFD-180/DuBeau
HFD-180/Duffy
HFD-180/Ysern
HFD-870/D.Lee
HFD-870/Sancho
JD/February 11, 1999 (drafted)
JD/2/11/99/c:\mydocs\nda\20884902-tcon.doc

APPEARS THIS WAY
ON ORIGINAL

TELECON

(8) DuBeau

MEMORANDUM OF TELECON

DATE: January 13 & 14, 1999

APPLICATION NUMBER: NDA 20-884; Aggrenox™ (dipyridamole/aspirin) Capsules

BETWEEN:

Name: Dr. David Brill; Director, Drug Regulatory Affairs
Phone: (203) 798-4340
Representing: Boehringer Ingelheim Pharmaceuticals, Inc.

AND

Name: Ms. Julieann DuBeau; Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Request for Additional Information

BACKGROUND:

Boehringer Ingelheim Pharmaceuticals, Inc. submitted NDA 20-884 on December 15, 1999. After the regulatory health project manager administratively reviewed the application and spoke with some of the application reviewers, the firm was contacted and requested to provide additional information.

TODAY'S PHONE CALL:

Dr. Brill was called and requested to provide the information listed below regarding NDA 20-884.

1. A revised overall index, sequential by volume number.
2. Race safety and efficacy analysis studies. Or alternatively, provide a written justification for not conducting the studies.
3. Written documentation regarding drug use in the pediatric population.
4. Unannotated labeling diskette in MS WORD 8.0.
5. Stability diskette in SAS data set format (9 month data).
6. PK/PD study summaries and results (tables/figures) in MS WORD 8.0.
7. Animal tumorigenicity study data in SAS data set format (biometric format).
8. SAS data sets and programs for safety and efficacy on CD for the statistician.
9. A written statement that all manufacturing facilities are ready for inspection.
10. A desk copy of volumes 1.001, 1.002, and 1.003 for the project manager.

Dr. Brill was informed that a meeting to determine the fileability of the application is tentatively scheduled for February 2, 1999, and that further information requests may be forthcoming. The call was then concluded.

FOLLOW-UP:

The following guidance was faxed to Dr. Brill on January 13, 1999, to assist him with #7 above: "Guidance for Industry: Statistical Aspects of Design, Analysis, and Interpretation of Animal Carcinogenicity Studies." [Draft, August 1997].

/S/ 1/22/99

APPEARS THIS WAY
ON ORIGINAL

Julieann DuBeau, RN, MSN
Regulatory Health Project Manager

cc: Original NDA 20-884
HFD-180/Div. File
HFD-180/DuBeau
JD/January 22, 1999 (drafted)
JD/1/22/99/c:\mydocs\20884901-tcon.doc

TELECON

APPEARS THIS WAY
ON ORIGINAL

CSO/DuBeau

NDA 20-884

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: David R. Brill, Ph.D.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

Dear Dr. Brill:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Aggrenox™ (dipyridamole/aspirin) Capsules

Therapeutic Classification: Priority (P)

Date of Application: December 15, 1998

Date of Receipt: December 15, 1998

Our Reference Number: 20-884

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 13, 1999, in accordance with 21 CFR 314.101(a). If the application is filed. the user fee goal date will be June 15, 1999.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, contact me at (301) 827-7310.

Sincerely,

APPEARS THIS WAY
ON ORIGINAL

Julieann DuBeau, RN, MSN
Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Archival NDA 20-884
HFD-180/Div. Files
HFD-180/J.DuBeau
DISTRICT OFFICE
JD/January 5, 1999 (drafted) /S/ 1/5/99
JD/1/5/99/c:\mydocs\20884901-ack.doc

ACKNOWLEDGEMENT (AC)

APPEARS THIS WAY
ON ORIGINAL

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	20884	**Trade Name:**	AGGRENOX(ASPIRIN 25MG/DIPYRIDAMOLE 200MG
Supplement Number:		**Generic Name:**	ASPIRIN/DIPYRIDAMOLE
Supplement Type:		**Dosage Form:**	EXC
Regulatory Action:	AP	**Proposed Indication:**	"To reduce the risk of stroke in patients who have had transient ischemia of the brain or completed ischemic stroke due to thrombosis."

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?
NO, Pediatric content not necessary because of pediatric waiver

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)
____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Adequacy Does Not Apply
Formulation Status
Studies Needed
Study Status

APPEARS THIS WAY ON ORIGINAL

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:
5/14/99. The Division recommends the following limited indication: "To reduce the risk of stroke in patients who have had transient ischemia of the brain or completed ischemic stroke due to thrombosis."

5/14/99: The firm's correspondence dated 1/18/99 states their peds plans as follows: "Please be advised that the sponsor has no plans to study the safety and effectiveness of Aggrenox in the pediatric age range in consideration of the draft indication statement."

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, JULIEANN DUBEAU

/S/
Signature

11/18/99
Date

APPEARS THIS WAY ON ORIGINAL

Boehringer Ingelheim

Boehringer Ingelheim
Pharmaceuticals, Inc.

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug
Products; HFD-180
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

January 18, 1999

Aggrenox (extended release dipyridamole 200 mg / aspirin 25 mg);
NDA 20-884/Amendment 003

David R. Brill, Ph.D.
Telephone (203)798-4340
Telefax (203)791-6180
E-Mail dbrill@bi-pharm.com

900 Ridgebury Rd/P.O. Box 368
Ridgefield, CT 06877-0368
Telephone (203) 798-9988
Telefax (203) 791-6234

Dear Ms. DuBeau:

Reference is made to the subject new drug application for Aggrenox™ that was submitted on December 15, 1998. In response to your request for information, Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI) is hereby submitting an amendment to NDA 20-884 for Aggrenox. The information being included within this amendment is described below.

Item 1: A revised Overall Index for the Aggrenox NDA which is organized and structured according to NDA Volume number (as opposed to NDA Section number).

Item 2: A single, additional CD (included as a desk copy) containing the SAS Transport Files as originally submitted within the CANDA for Aggrenox.

Item 3: A single, diskette (included as a desk copy) containing the unannotated package insert in a format that is compatible to MS Office 97.

In addition to the information being included above, BIPI was requested to provide information regarding the plans for pediatric studies with Aggrenox. Please be advised that the sponsor has no plans to study the safety and effectiveness of Aggrenox in the pediatric age range in consideration of the draft indication statement. Specifically, the drug is to be recommended for patients at risk for stroke (i.e. those with a recent ischemic stroke or transient ischemic attack). The sponsor believes that such patients in the pediatric age range are extremely rare and thus there are no plans to specifically study the use of Aggrenox in the pediatric population. Additionally, the sponsor believes that the use of aspirin in patients less than 12 years of age are at risk for

Boehringer Ingelheim

development of Reyes syndrome and is an additional reason for the lack of plans to study Aggrenox in the pediatric age range.

Finally, BIPI was requested to comment upon the availability of an efficacy and safety analysis for the subgroups of age, gender and race within the ESPS 2 trial. Please be advised that with regard to age and gender, the efficacy analysis can be found within NDA section 8.8.3, NDA volume 1.087, starting on page 218. The safety analysis for these subgroups can be found within NDA section 8.9.2.12, NDA volume 1.090, starting on page 158. No information regarding race was collected as part of this European phase III trial.

The additional information you requested is in the process of being compiled and will be submitted as soon as it is available. If you have any questions or comments on the information included within this amendment, please call me directly.

Sincere regards,

David R. Brill

David R. Brill, Ph.D.
Director, Drug Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

CDER LABELING AND NOMENCLATURE COMMITTEE

CONSULT #	1185	HFD#	180	PROPOSED PROPRIETARY NAME:	PROPOSED ESTABLISHED NAME:
ATTENTION:	Julieann Dubeau			AGGRENOX	dipyridamole and aspirin capsules

A. Look-alike/Sound-alike

	Potential for confusion:
ALCONOX	xxx Low ____ Medium ____ High
	____ Low ____ Medium ____ High
	____ Low ____ Medium ____ High
	____ Low ____ Medium ____ High
	____ Low ____ Medium ____ High

B. Misleading Aspects:

C. Other Concerns:

D. Established Name

xxx Satisfactory

____ Unsatisfactory/Reason

Recommended Established Name

E. Proprietary Name Recommendations:

XXX ACCEPTABLE ____ UNACCEPTABLE

F. Signature of Chair/Date /S/ 5/14/99

Memorandum

Date: 22 November 1999

From: David E. Morse, Ph.D. /S/
Asc. Director (Pharm./Tox.), Office of Drug Evaluation III

To: Florence Houn, M.D.
Director, Office of Drug Evaluation III

Cc: Lillia Talarico, M.D., Dir., DGCDP (HFD-180)
Jasti Choudary, Ph.D., TL Pharm./Tox., DGCDP (HFD-180)
Ke Zhang, Ph.D., Pharm./Tox., DGCDP (HFD-180)

Subject: NDA 20-884
AGGRENOX® (dipyridamole and aspirin)
Review of Pharm./Tox. Information and Sections of Proposed Product Label

I. Materials Included in Review

1. Pharm./Tox. Reviews of NDA 20-884, dated 9 Nov., 20 and 8 Sept., and 30 April 1999, written by Ke Zhang, Ph.D.
2. NDA 20-884 Approval Package with Draft Product Labeling (dated 16 Nov. 1999).

II. Comments and Conclusions

1. A review of the action package for NDA 20-884, AGGRENOX®, suggests that the product has been adequately evaluated in multiple non-clinical safety studies (including carcinogenicity studies conducted with dipyridamole) for approval of the requested indication (to reduce the risk of stroke in patients who have had transient ischemia of the brain or completed ischemic stroke due to thrombosis). The proposed product labeling adequately reflects the toxicological findings for dipyridamole/aspirin regarding carcinogenesis, mutagenesis, fertility, pregnancy and overdosage.

2. Specific comments related to the product label follow:
   - Reference to the brand name for dipyridamole (i.e., PERSANTINE®) should be eliminated from the discussion of all non-clinical studies in the product label, unless those studies were specifically conducted with the marketed drug formulation. All discussions of non-clinical studies conducted with other than the clinical drug formulation should make reference to the generic compound name of 'dipyridamole.'
   - It is recommended that all interspecies dose comparisons included in the product label be based on pharmacokinetic parameters (i.e., AUC, C_{max} or other relevant parameter) unless there is clear scientific justification for the use of another scaling method (i.e., allometric scaling or nominal dose), or there is insufficient pharmacokinetic data to allow for interspecies dose comparisons.
   - While interspecies dose comparisons may be performed based on body-surface-area adjusted doses, in accordance with Pharm./Tox. Policy (PTCC Meeting of June 1999), the computed mg/m^2 dose for the animals should not be presented in the product label. Instead, only the relative interspecies dose comparison should be presented in the product label (e.g., Reproduction studies with dipyridamole revealed

no evidence of impaired fertility in rats at doses up to 500 mg/kg/day, approximately 10 times the human dose on a body surface area basis.). Deletion of the mg/m^2 doses should be performed for all animal studies presented in the label sections on Carcinogenesis, Mutagenesis, Impairment of Fertility, and Pregnancy.

- Under the heading of "Overdosage," it is suggested that the single dose study conducted in rats with the combination drug product (dipyridamole and aspirin) provides minimal information, given the clinical overdosage data available/included for the individual drug products. Consideration should be given to the deletion of the overdosage statement for the combination drug product as tested in rats, and listed under the heading "AGGRENOX." If this statement is retained in the product label, then the multiplicity of human exposure achieved in the rat study should also be presented (BSA adjusted or AUC based).

3. If the data are available, consideration should be given to the inclusion of information on breast milk drug concentration and potential neo-natal drug exposure in woman administered AGGRENOX® during lactation.

APPEARS THIS WAY
ON ORIGINAL

Summary

A review of the action package for NDA 20-884, AGGRENOX®, suggests that the product has been adequately evaluated in multiple non-clinical safety studies for approval of the requested indication. The proposed product label, with possible revision as suggested in the preceding section, adequately reflects the safety data for this product.

APPEARS THIS WAY
ON ORIGINAL