CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020884

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

NOV 1 2 1999

Pharmacometrics Consult Review

NDA:	20-884 amendment 028
Dipyridamole 200 mg/ASA 25 mg ER Capsules (Aggrenox®)	
Original Submission Date:	3 November, 1999
Sponsor:	Boehringer Ingelheim
Type of Submission	Population PK Analysis – Response to Request for Information
Received by Pharmacometrics:	11/4/99
Primary Reviewer:	Alfredo Sancho
Medical Division:	HFD-180 (GI/Anticoagulation)
Pharmacometrics Scientist:	Michael J. Fossler

Submission

At the request of the primary reviewer, Pharmacometrics has reviewed the population PK analysis submitted with NDA 20-884, ***ESPS 2 – Secondary European Stroke Prevention Study – a double-blind, randomized, placebo-controlled, multi-center study of four parallel groups organized in a 2x2 factorial design.*** The firm has supplied the requested information in order to facilitate the review. In addition, Pharmacometrics has located the original study report for this analysis, which was contained in volume 1.071 of the original NDA.

Study Design

This was a randomized, double-blind, placebo-controlled parallel-group, multi-center study in patients who had suffered a previous CVA within the past three months. The patients were randomized to one of four treatment groups:

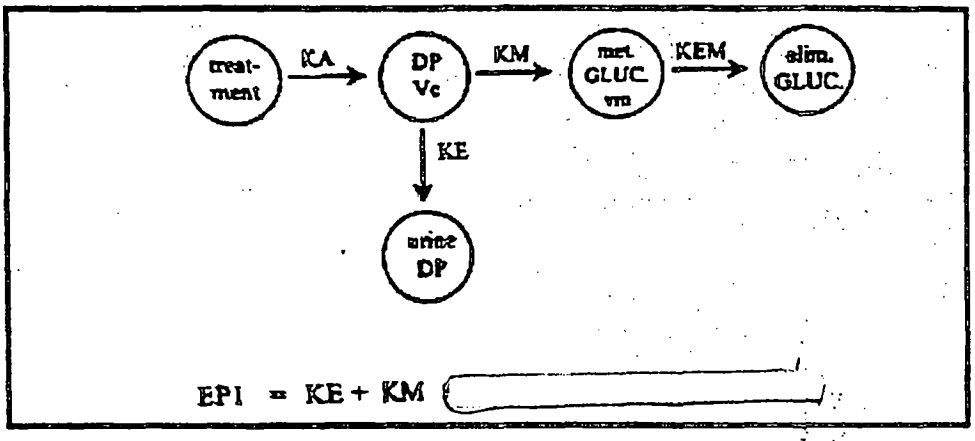
- Persantine ER 200 mg
- ASA 25 mg
- Aggrenox 200/25 mg
- placebo

A subset of the total number of patients (n=404) were included in the population analysis. From this sub-set, a single plasma sample was drawn from each subject in order to assess compliance. These samples were then used in a retrospective population PK analysis to evaluate the effects of co-variates such as age, weight, gender, duration of treatment, type of treatment, and creatinine clearance on the PK of dipyridamole (DP) and its glucuronide conjugate (DP-G).

The population analysis was performed using [redacted]. A simple one compartment model was used to determine the PK of DP and DP-G. A depiction of the model is shown in Figure 1. Since only 1 sample per subject was available, no estimates of inter-individual variability could be obtained Dipyridamole and its glucuronide conjugate were fitted simultaneously. Since it was known from previous studies that ~95% of a dose is excreted as the glucuronide, this prior information was incorporated into the model.

The procedure followed for examining covariates was the usual approach. A base model was fitted (without covariates). On the basis of diagnostic plots, covariates were added to the model. [redacted]

*Figure 1: Pharmacokinetic Model used in the analysis. KA – absorption rate constant, KE – renal elimination rate constant of parent, KM – metabolic elimination rate constant of parent, KEM – elimination rate constant of glucuronide. Im this model, CL/F of parent = (EP1)*Vc, where EP1 = KE+KM.*



Results

Table 1 shows the pivotal runs performed during the development of the final model, with the corresponding objective function values. The covariate that has the largest potential impact on the pharmacokinetics of dipyridamole and its glucuronide is age. The parameter results are shown in Table 2. As seen in Figure 2, the clearance of DP in patients less than 55 years of age is nearly twice that seen in patients aged 65 or greater. The impact on the glucuronide is similar (data not shown). Weight appears to be an important predictor of clearance as well (Figure 3). Although the effect of gender is statistically significant, its actual magnitude is quite small (Figure 4) and is probably not clinically significant.

Table 2: Mean population parameter estimates for the final model.

Parameter	Typical value	Theta estimates
$KM = 0.95*\theta_1*\theta_9**SEX*(AGE/50)**\theta_4$	males: 0.0659 hr^{-1} females: 0.0602 hr^{-1}	θ_1: 0.0951 θ_9: 0.9119 θ_4: -1.199
$KE = 0.05*\theta_1*(AGE/50)**\theta_7$	3.937 x 10^{-3} hr^{-1}	θ_1: 0.0951 θ_7: -0.7189
$KEM = \theta_6*(AGE/50)**\theta_{11}$	4.27 hr^{-1}	θ_6: 5.59 θ_{11}: -1.303
$KA = \theta_3$	1.34 hr^{-1}	—
$V_c = \theta_2 + WGT*\theta_8$	158.9 L	θ_2: 106.5 θ_8: 0.716
$V_m = \theta_5 + WGT*\theta_{10}$	6.98 L	θ_5: 3.499 θ_{10}: 0.0475
σ_{DP}	†23.8% (48.8%)	–
σ_{DP-G}	†59.2% (76.9%)	–

†residual variability estimates (precision of estimate)

Figure 2: CL/F of dipyridamole as a function of age. Open circles show the individual values, while the horizontal lines depict the means.

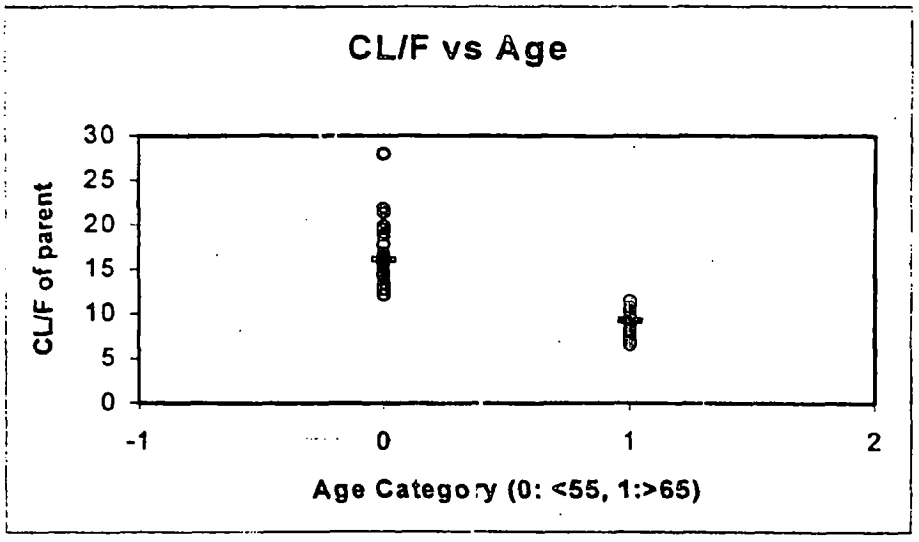


Figure 3: CL/F of dipyridamole as a function of weight.

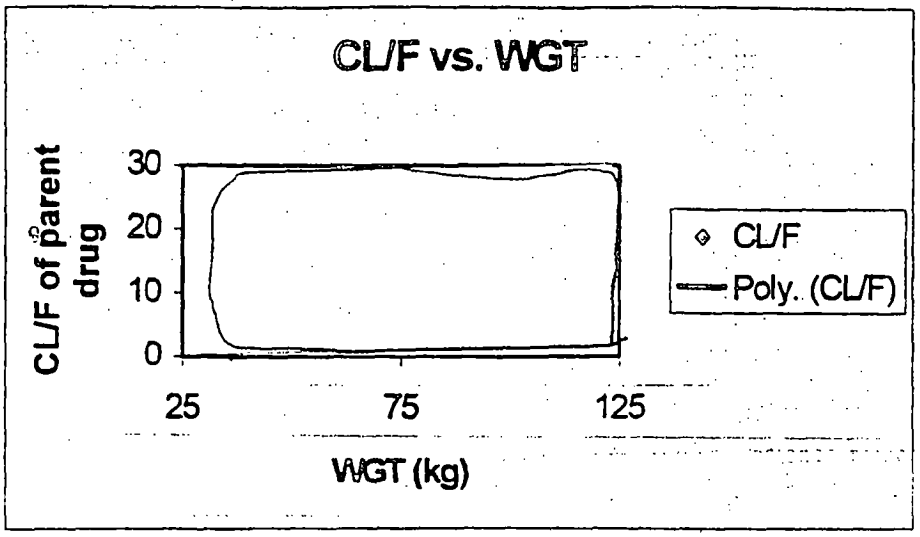
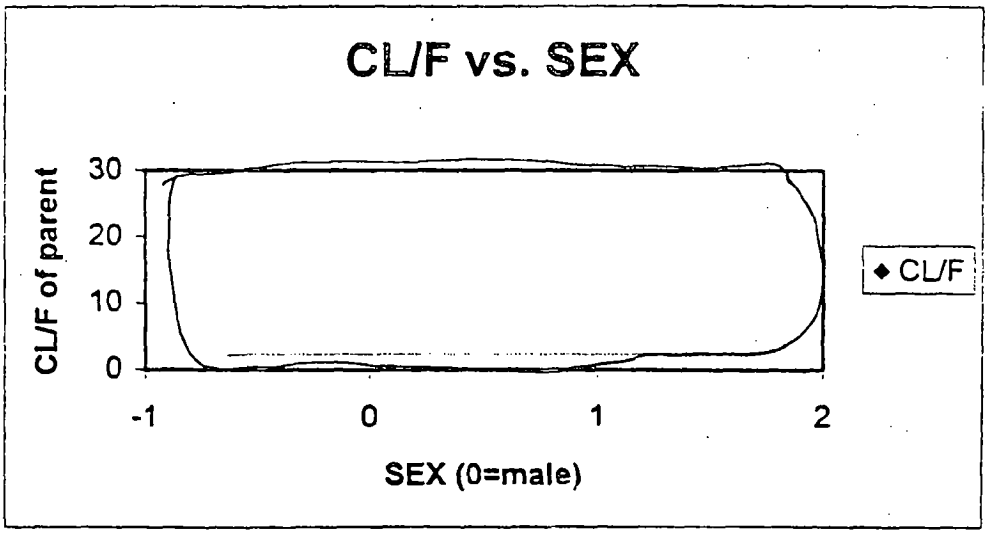


Figure 4: CL/F of dipyridamole as a function of sex



The effect of age on clearance, if real, might be clinically important because of its magnitude. Since the study utilized only one data point per individual, the overall conclusions from this study must be treated with some care. Also, the firm correctly points out that there are very few data for subjects less than 50 years of age, so that this too, must be taken into consideration when interpreting these data. Nevertheless, these data at least raise the possibility that younger subjects might be inadequately treated with dipyridamole, due to increased clearance of the drug. This should be further investigated in a more definitive study, as there are no data on the effect of age in the original Persantine labeling.

Comments to Medical Reviewer

- Based on limited data, it appears that age may have a significant effect on dipyridamole clearance. This means that younger patients treated with this product are effectively receiving 40% less drug than patients that are aged 65 or greater. Are there sufficient data in the NDA in subjects < 55 to make a determination as to whether or not comparable efficacy is seen in these two age groups? Because of the magnitude of the effect, (40%) and the potential for severe consequences should patients be under-dosed, would an adjustment of dose in younger subjects be a reasonable course of action to pursue until a more definitive study is conducted?

Reviewer Conclusions

- Weight, age and gender appear to affect the clearance of dipyridamole and its glucuronide metabolite; however, only age appears to reach a magnitude that could be clinically significant.
- The firm should perform a definitive study examining the effect of age on the pharmacokinetics of dipyridamole/ASA. The age range to be studied should conform to that seen in the ESPS2 trial. This should be performed as a Phase 4 commitment, unless HFD-180 feels that the data are necessary before approval. The firm should be encouraged to consult OCPB regarding the study design.

Labeling Comments

1) The changes submitted in Attachment 3 of the amendment dated 11/4/99 are acceptable.

2) The text under ***Special Populations:*** *Geriatric Patients* should be modified as follows:

Special Populations: *Geriatric Patients* : In ESPS2 (See CLINIAL PHARMACOLOGY, Clinical Trials) the mean clearance of dipyridamole in younger patients (< 55 years) was 40% higher than that seen in elderly patients (> 65 years). This clinical significance of this finding is unclear.

/S/ 11/12/99

Michael J. Fossler, Pharm.D., Ph.D.

Pharmacometrics Scientist
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

APPEARS THIS WAY
ON ORIGINAL

CC: NDA 20-884(orig., 1 copy), HFD-850(Lee, Lesko), HFD-870(M. Chen, Fossler, Lee, Sancho)

OCT 26 1999

Memorandum
Clinical Pharmacology and Biopharmaceutics Review

NDA 20-884

Drug Name: Aggrenox (200 mg/25 mg Capsules) Ref.: Revised Aggrenox label.

Submission Date: August 06 1999 (Amendment no. 23).

Sponsor: Boehringer Ingelheim, Inc.
Sponsor's Address: 900 Ridgebury Rd., P. O. Box 368, Ridgefield, CT 06877-0368

SYNOPSIS

The sponsor on August 06 1999 submitted a revision to the proposed drug product label. This version dated 8-6-99 includes the Agency recommendations faxed to the sponsor on 6-15-99.

RECOMMENDATION

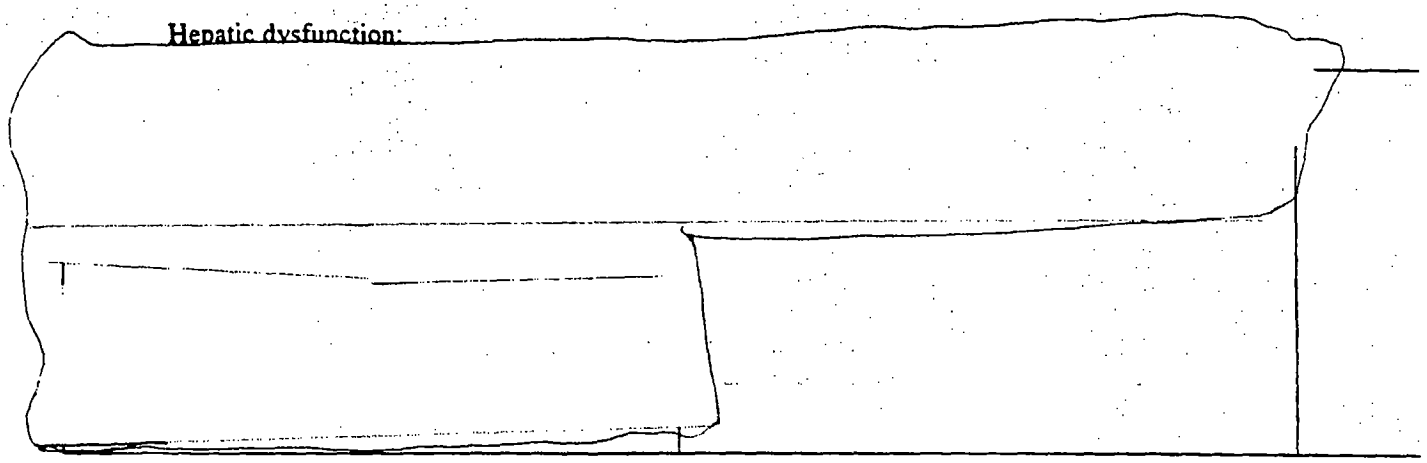
The Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation II has reviewed the proposed drug product label submitted to the Agency on August 06, 1999. Some of the labeling wording has been constructed from the ESPS2 Population Pharmacokinetic analysis. This Population Pharmacokinetic assessment was consulted to the Pharmacometrics Scientist, Dr. Mike Fossler, on 01 October 1999. Based upon an evaluation of the provided information, including the results from the Pharmacometrics consult, the following are the recommended changes for the Clinical Pharmacology section of the drug product label:

1. Special Populations Section

Geriatric Patients

Renal dysfunction:

Hepatic dysfunction:



/S/ 26 Oct 99

APPEARS THIS WAY
ON ORIGINAL

Alfredo R. Sancho, Ph.D.
Clinical Pharmacology and Biopharmaceutics Reviewer
Radiopharmaceutical and Medical Imaging Division
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

Concurrence:

/S/ 10/26/99

APPEARS THIS WAY
ON ORIGINAL

David J. Lee, Ph.D.
Team Leader
Radiopharmaceutical and Medical Imaging Division
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

Cc: HFD-180 NDA20-884 (1x), DIV.FILE (1x); DUBEAU (1X); SANCHO (1X); LEE (1X)
HFD-870 JHUNT (1x); MLCHEN (1x)
HFD-850 SHUANG
CDR Attn.: Barbara Murphy

Attachment: Pharmacometrics consult.

TECHNICAL BACKGROUND

Aggrenox is a combination drug product 200-mg/25-mg, respectively, of dipyridamole [2,6-bis-(diethanol-amino)-4,8-dipiperidino-pyrimido-(5,4-d) pyrimidine] and aspirin [Benzoic acid, 2-(acetyloxy)-salicylic acid acetate].

Dipyridamole (DP) is an antiplatelet agent with a molecular weight of 504.63 and the chemical formula, $C_{24}H_{40}N_8O_4$. Dipyridamole is an odorless yellow crystalline substance, having a bitter taste. It is soluble in dilute acids, methanol, and chloroform, while it is insoluble in water.

Aspirin or Acetylsalicylic Acid (ASA) is also an antiplatelet agent with a molecular weight of 180.16 and the chemical formula, $C_9H_8O_4$. ASA is an odorless white, needle-like crystalline or powdery substance. When exposed to moisture, it hydrolyzes into salicylic and acetic acids, giving off a vinegary odor. It is highly lipid soluble and slightly soluble in water.

APPEARS THIS WAY
ON ORIGINAL

DuBEAN

OCT 26 1999

Memorandum
Clinical Pharmacology and Biopharmaceutics Review

NDA 20-884

Drug Name: Aggrenox (200 mg/25 mg Capsules) Ref.: Sponsor's Response to IR letter.

Submission Date: August 20 1999.

Sponsor: Boehringer Ingelheim, Inc.
Sponsor's Address: 900 Ridgebury Rd., P. O. Box 368, Ridgefield, CT 06877-0368

SYNOPSIS

The Agency communicated on June 15 1999 five (5) issues regarding Clinical Pharmacology and Biopharmaceutics. This was followed by a meeting request from the sponsor (June 30 1999), a pre-meeting fax to the sponsor (July 27 1999), and the meeting on August 03 1999. On August 20 1999, the sponsor submitted a response to these concerns. Summaries of these five concerns and the actions taken upon these concerns are:

Item 1 - *Bioequivalence between the to-be-marketed Aggrenox capsules and all clinical trial formulations or batches.*

This item was discussed in detail during the 03 August 1999 meeting. Please see details in the meeting's minutes.

Item 2 - *A new and more appropriate dissolution method using the intact to-be-marketed product.*

A new dissolution method and dissolution testing of the intact to-be-marketed drug product was agreed. The sponsor submitted the description of the new dissolution method, as well as the results, dissolution profile, of the intact to-be-marketed drug product.

Item 3 - *A food-effect study using the to-be-marketed product.*

The sponsor agreed to conduct a food-effect study, to be conducted independently from the extended release study. On August 11 1999, the sponsor submitted the protocol for this study. It has been reviewed (by Dr. Ron Kavanagh) and comments have been sent to the sponsor. The Agency is waiting to receive the revised food-effect protocol from the sponsor.

Item 4 - *An extended-release study using the to-be-marketed product.*

The sponsor agreed to conduct an extended-release study, independent from the food effect study. On August 20 1999, they submitted the proposed protocol for this study. It has been reviewed and comments have been sent to the sponsor. Overall, the sponsor's proposed protocol is adequate.

Item 5 - *A population pharmacokinetic analysis of the ESPS-2 data.*

The data and a report from the sponsor on their conclusions from the data was submitted on August 20 1999. Both of these items have been forwarded to the Pharmacometrics scientist (Dr.

Mike Fossler) for a consult. The Pharmacometrics scientist has concluded that there was no output nor suitable data included in the submission, it is impossible to evaluate these results. No use of these results in labeling should be permitted until the firm submits the following information (**see attached copy of resulting Pharmacometrics consult**):

- Study data in NONMEM-ready format,
- Pivotal output from NONMEM runs, and
- Goodness-of-fit plots for final model.

DISCUSSION

The following drug product batches were tested using the new dissolution method:

Batch No.	Source*
807443, 807444	12 and 15 month stability batches, respectively
710187, 30104	Bioequivalence study
907567, 907568, 907570, 907571, 907572	Batches intended for direct market supply in the USA

* No samples of the pivotal clinical batches were available for these dissolution studies.

The time points for the new dissolution method are 1, 2, 5, and 7 hours. In the description of the new dissolution method, the sponsor refers to the proposed drug product (200/25 mg Dipyridamole/Acetylsalicylic acid capsule or Asasantine ER capsules) as "R-A 8 BS". The sponsor's new dissolution method is described as follows:

1. Test Solution A
   - Place 1 capsule in each of 6 baskets.
   - Slowly lower the basket with the shaft into the test vessel, which contains 900.0 ml of 0.1N hydrochloric acid at 37°C (±0.5 °C), in such a way that air bubbles are not formed on the surface of the capsule.
   - A distance of 2.5 cm (±0.2 cm) is maintained between the bottom of the basket and the inside bottom of the vessel throughout the test.
   - With the aid of the electric motor, operate the apparatus at 100 rpm (±4%).
   - One hour after the start of rotation, withdraw a 10.0 ml sample by pipette through a porosity 2 sintered glass immersion filter from a zone midway between the surface of the dissolution medium and the top of the basket, not less than 2 cm from the vessel wall.
   - Filter the sample through a pleated filter paper.
   - Dilute 1.0 ml to 5.0 ml with 0.1 N hydrochloric acid.
   - Then remove the basket from the vessel and take the steel plug out of the vent.
   - Carefully immerse the basket once in 80.0 ml of water contained in a 100 ml glass beaker and, after the water has drained from the basket, re-seal the vent with the steel plug and carry out the procedure as described under "Test solution B".
2. Test Solution B
   - Lower each of the 6 baskets into separate 1000 ml test vessels containing 900.0 ml of phosphate buffer solution pH 5.5 at 37 °C (±0.5 °C).
   - Using the same setting and the same conditions, proceed as described for test solution A.

- After the specified time intervals, withdraw 2.0 ml from each vessel through a porosity 2 sintered glass immersion filter as described in test solution A.
- Dilute 1.0 ml to 5.0 ml with 0.1N hydrochloric acid.
- Replace each quantity of solution withdrawn with the same quantity of phosphate buffer solution pH 5.5 at 37 °C.

3. Standard solution
   - Dissolve about 22.2 mg of R-A 8 BS reference standard, accurately weighed, in 100.0 ml of 0.1N hydrochloric acid.
   - Dilute 10.0 ml to 50.0 ml with 0.1N hydrochloric acid.
4. Determination
   - Test solution A
     - Using a suitable spectrophotometer, measure the absorbance of test solution A and the standard solution in 1 cm cells against 0.1N hydrochloric acid at the maximum at about 405 mm.
   - Test solution B
     - Using a suitable spectrophotometer, measure the absorbance of test solution A and the standard solution in 1 cm cells against 0.1N hydrochloric acid at the maximum at about 405 mm.
5. Calculation

% of R-A 8 BS released in 1st hour

$$= \frac{ATA \times WtRS \times 10 \times 900 \times 5 \times 100 \times C}{AS \times DC \times 100 \times 50 \times 1 \times 1 \times 100}$$

$$= \frac{ATA \times WtRS \times 9 \times C}{AS \times DC}$$

Where,
ATA = absorbance of test solution A
AS = absorbance of standard solution
WtRS = weight of R-A 8 BS reference standard used to prepare standard solution (mg)
DC = declared active ingredient content/capsule (mg)
C = percentage content of reference standard used

% of R-A 8 BS released after specified time intervals

$$= \frac{ATB \times WtRS \times 10 \times 900 \times 5 \times 100 \times C}{AS \times DC \times 100 \times 50 \times 1 \times 1 \times 100} + \% \text{ released in } 1^{st} \text{ hour}$$

$$= \frac{ATB \times WtRS \times 9 \times C}{AS \times DC} + \% \text{ released in } 1^{st} \text{ hour}$$

Where,
ATB = absorbance of test solution B
AS = absorbance of standard solution
WtRS = weight of R-A 8 BS reference standard used to prepare standard solution (mg)
DC = declared active ingredient content/capsule (mg)
C = percentage content of reference standard used

The release of R-A 8 BS can also be determined with the aid of an automatic _____ release apparatus. If this apparatus is used, the release values should be calculated using the E 1% value instead of the absorbance of the standard solutions.

COMMENTS

1. The dissolution data of the intact to-be-marketed drug product batches, using the new dissolution method, provided the requested dissolution profile information. Several batches were included in this testing, including two batches (710187, 30104) from the bioequivalence study; but no samples of the pivotal clinical batches were available for these dissolution studies. The batches tested using this new dissolution method have similar dissolution profiles.
2. The sponsor also executed the same dissolution testing on another series capsules from the same batches. These second set of capsules did not contain the ASA tablet. The Dipyridamole percent release in each of the six vessels and their mean values, are similar to that of the intact capsules. Based on both the dissolution profiles of the intact capsule and the capsule without the ASA tablet, using the new dissolution method, it seems that the absence or presence of ASA does not affect the dissolution profile of DP pellets under these conditions.
3. The Population Pharmacokinetic information, data, and conclusions submitted by the sponsor were sent for a consult to the Pharmacometrics scientist. In response to the requested consult, it is concluded that insufficient information has been provided in the submission; therefore, the results stated by the sponsor can not be used in the labeling of this drug product. The comments from the Pharmacometrics consult and the information needed to address the deficiencies should be forwarded to the sponsor.

RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation II has reviewed the information included in the sponsor's re-submission of August 20 1999. Based upon an evaluation of the provided information and data it is concluded that:

The sponsor has properly addressed some of the issues (items 1 through 4) discussed in this document. There are deficiencies in the Population Pharmacokinetics information (item 5) submitted by the sponsor. The comments and information request in the Pharmacometrics consult relating to the Population Pharmacokinetics should be forwarded to the sponsor.

/S/

Alfredo R. Sancho, Ph.D.
Clinical Pharmacology and Biopharmaceutics Reviewer
Radiopharmaceutical and Medical Imaging Division
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

Concurrence:

/S/ 10/26/99

David J. Lee, Ph.D.
Team Leader
Radiopharmaceutical and Medical Imaging Division
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

Attachment: Pharmacometrics consult results.

Pharmacometrics Consult Review

NDA:	20-884
Dipyridamole 200 mg/ASA 25 mg ER Capsules (Aggrenox®)	
Original Submission Date:	
Sponsor:	Boehringer Ingelheim
Type of Submission	Population PK Analysis
Received by Pharmacometrics:	10/1/99
Primary Reviewer:	Alfredo Sancho
Medical Division:	HFD-180 (GI/Anticoagulation)
Pharmacometrics Scientist:	Michael J. Fossler

Submission

At the request of the primary reviewer, Pharmacometrics has reviewed the population PK analysis submitted with NDA 20-884, ***ESPS 2 – Secondary European Stroke Prevention Study – a double-blind, randomized, placebo-controlled, multi-center study of four parallel groups organized in a 2x2 factorial design.***

Study Design

This was a randomized, double-blind, placebo-controlled parallel-group, multi-center study in patients who had suffered a previous CVA within the past three months. The patients were randomized to one of four treatment groups:

- Persantine ER 200 mg
- ASA 25 mg
- Aggrenox 200/25 mg
- placebo

A subset of the total number of patients (n=404) were included in the population analysis. From this sub-set, a single plasma sample was drawn from each subject. These samples were then used in a population PK analysis to evaluate the effects of co-variates such as age, weight, gender, duration of treatment, type of treatment, and creatinine clearance on the PK of dipyridamole (DP) and its glucuronide conjugate (DP-G).

The population analysis was performed using [redacted] A simple one compartment model was used to determine the PK of DP and DP-G. None of the NONMEM runs were submitted for evaluation by Pharmacometrics. Data were supplied by the firm, but it was not in NONMEM format.

Results

The firm states that age, weight and gender were found to influence the PK of DP and DP-G. Of these, age showed the most pronounced effect, with clearance declining by 30-40% in patients older than 65 as compared with patients 55 years old or younger. The weight and gender differences seen were much more modest. Women had clearance values that were on average 8% lower than men . Clearance was found to be dependent on body weight, with patients weighing less than 67 kg having values 14-18% lower than heavier patients.

The effect of age on clearance, if real, might be clinically important. Since none of the NONMEM output was supplied, and since [redacted] were not supplied, it is impossible for Pharmacometrics to evaluate the validity of these findings.

Reviewer Conclusions

- Since no output nor suitable data were included in the submission, it is impossible to evaluate these results. No use of these results in labeling should be permitted until the firm submits the following:

  - Study data in [redacted]
  - Pivotal output from [redacted]
  - Goodness-of-fit plots for final model

/S/ 10/21/99

APPEARS THIS WAY
ON ORIGINAL

Michael J. Fossler, Pharm.D., Ph.D.

Pharmacometrics Scientist
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

CC: NDA 20-884(orig., 1 copy), HFD-850(Lee, Lesko), HFD-870(M. Chen, Fossler)

APPEARS THIS WAY
ON ORIGINAL

DRAFT-1

OCT 15 1999

Memorandum
Clinical Pharmacology and Biopharmaceutics Review

NDA 20-884

Drug Name: Aggrenox (200 mg/25 mg Capsules) Ref.: Extended Release Protocol

Sponsor: Boehringer Ingelheim, Inc.

Sponsor's Address: 900 Ridgebury Rd., P. O. Box 368, Ridgefield, CT 06877-0368

SYNOPSIS

The Agency communicated on June 15, 1999 five (5) issues regarding Clinical Pharmacology and Biopharmaceutics. Summaries of these five concerns are:

1. *Bioequivalence between the to-be-marketed Aggrenox capsules and all clinical trial formulations or batches;*
2. *A new and more appropriate dissolution method using the intact to-be-marketed product;*
3. *A Food-effect study using the to-be-marketed product;*
4. *An Extended-release study using the to-be-marketed product;* and,
5. *A Population pharmacokinetic analysis of the ESPS-2 data.*

On August 20, 1999, the Sponsor submitted a response to these concerns. The intent of the current memorandum is to provide the sponsor comments on the Extended Release protocol using the to-be-marketed product that was submitted on August 20, 1999.

GENERAL COMMENTS

The present Extended-Release study protocol is intended to compare the b.i.d. treatment regimen for Aggrenox to an FDA approved immediate release Persantine tablet and Aspirin tablets; specifically, to assess the drug exposure to patients following the reduced dosing regimen of Aggrenox.

Study Design:

Two-way crossover study in 18 healthy subjects. (Age: 18-55 years; Gender: males and females)

Treatments:

Treatment A	Aggrenox b.i.d. (200 mg dipyramidole ER + 25 mg ASA IR)
Treatment B	2x50 mg Persantine IR q.i.d. + 25 mg ASA b.i.d.

Dosing Regimen:

Treatment A	8 am and 6 pm
Treatment B	Persantine - 8 am, 1 pm, 6 pm, and 11 pm ASA - 8 am and 6 pm

Details:

- There will be four "loading" days.
- Intake will be with 180 ml of water under "fasting" conditions
- "Normal" meals will be provided 0.5 hrs post-dosing

Sampling:

- Pre-dose blood sampling and on days 1, 2, 3, and 4.
- Day 5 sampling scheme:

0, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12

- 24 and 48 post-dosing

Urine samples will be obtained on day 5 for 0-10 hrs for both treatments

Primary Endpoints:

The sponsor states that it is to analyze serial dipyridamole concentrations in order to evaluate the PK based on confidence intervals of AUCss and %peak-trough fluctuation (%PTF) at log-normal scale.

Secondary Endpoints:

Pk of dipyrimadole at Steady-State (C_{max}, C_{max}/AUC, T_{max}, AUC, $t_{1/2}$, and Ae% of dp and dp-gluc).

PK of ASA (Ae%).

COMMENTS

1. The sponsor should clarify if the Aggrenox product to be used in this Extended-Release study is that of the to-be-marketed formulation.

RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics Division of Pharmacological Evaluation II has reviewed the Extended Release protocol (with the to-be-marketed product) included in the re-submission of August 20, 1999. Based upon an evaluation of the provided information and data it is concluded that:

There are no concerns or objections with respect to the Extended-Release study protocol provide by the sponsor. The statement in the Comment section of this document should be forwarded to the sponsor for response.

/S/ 10-15-99

Alfredo R. Sancho, Ph.D.
Clinical Pharmacology and Biopharmaceutics Reviewer
Radiopharmaceutical and Medical Imaging Division
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

APPEARS THIS WAY
ON ORIGINAL

Concurrence:

APPEARS THIS WAY
ON ORIGINAL

/S/ 10/15/99

David J. Lee, Ph.D.
Team Leader
Radiopharmaceutical and Medical Imaging Division
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

Cc: HFD-160 NDA20-884 (1x); DIV.FILE (1x); DUBEAU (1X); SANCHO (1X); LEE (1X)
HFD-870 JHUNT (1x); MLCHEN (1x)
HFD-850 SHUANG
CDR Attn.: Barbara Murphy

APPEARS THIS WAY
ON ORIGINAL

SEP - 3 1999

Memorandum
Clinical Pharmacology and Biopharmaceutics Review

NDA 20-884

Drug Name: Aggrenox (200 mg/25 mg Capsules) Ref.: Resubmission

Sponsor: Boehringer Ingelheim, Inc.

Sponsor's Address: 900 Ridgebury Rd., P. O. Box 368, Ridgefield, CT 06877-0368

SYNOPSIS

The Agency communicated on June 15, 1999 five (5) issues regarding Clinical Pharmacology and Biopharmaceutics. Summaries of these five concerns are:

1. *Bioequivalence between the to-be-marketed Aggrenox capsules and all clinical trial formulations or batches;*
2. *A new and more appropriate dissolution method using the intact to-be-marketed product;*
3. *A Food-effect study using the to-be-marketed product;*
4. *An Extended-release study using the to-be-marketed product;* and,
5. *A Population pharmacokinetic analysis of the ESPS-2 data.*

On August 20, 1999, the Sponsor submitted a response to these concerns. The intent of the current memorandum is to state briefly, after a cursory review, what information was found in the Sponsor's re-submission to address the above five issues. Further review of the re-submission information will be needed to assess the quality of the information and the appropriateness to address the fore mentioned five issues.

GENERAL COMMENTS

3. *Food-effect information*: A Food-effect protocol was forwarded by the sponsor in an earlier communication dated August 12, 1999.

4. *Extended-release information*: An Extended-release protocol has been provided by the sponsor in the current re-submission package.

5. *Population PK information*: A diskette labeled "Population PK data from ESPS2" was submitted. It will be forwarded to the designated Pharmacometric scientist for complete review.

RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics Division of Pharmacological Evaluation II has reviewed the re-submission information and data submitted August 20, 1999. Based upon an evaluation of the provided information and data it is concluded that:

The Sponsor has provided information and data addressing the five issues in the "Biopharmaceutics Section" of the Agency's letter dated June 15, 1999. A cursory review was conducted at this time and it appears that the re-submission package contains information to begin a review. However, further detailed review is needed to assess the appropriateness of the information and data provided by the sponsor.

/S/ 03/Sep/99

Alfredo R. Sancho, Ph.D.
Clinical Pharmacology and Biopharmaceutics Reviewer
Radiopharmaceutical and Medical Imaging Division
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

APPEARS THIS WAY ON ORIGINAL

Concurrence:

/S/ 9/3/99

David J. Lee, Ph.D.
Team Leader
Radiopharmaceutical and Medical Imaging Division
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

Cc: HFD-160 NDA20-884 (1x); DIV.FILE (1x); DUBEAU (1X); SANCHO (1X); LEE (1X)
HFD-870 JHUNT (1x); MLCHEN (1x)
HFD-850 SHUANG
CDR Attn.: Barbara Murphy

DuBeau

Clinical Pharmacology and Biopharmaceutics Review

JUN 15 1999

NDA 20-884

Title: AGGRENOX™ ER (extended release dipyridamole 200 mg and immediate release aspirin 25 mg) Capsules

Serial No.: 000 Submission Date: 15 December 1998 Reviewer: David J. Lee, Ph.D.

Dosage: Oral administration capsules *b.i.d.* Review Date: June 15, 1999

Indications:

Sponsor: Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI)

900 Ridgebury Road, P. O. Box 368, Ridgefield, CT 06877

Type of Review: Original NDA 1P – Labeling Comments

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) has reviewed the proposed Aggrenox labeling by the Applicant. Since there are many clinical pharmacology and biopharmaceutical issues/deficiencies with this NDA submission, the Aggrenox labeling needs major modification by the Applicant, except for the Mechanism of Action section.

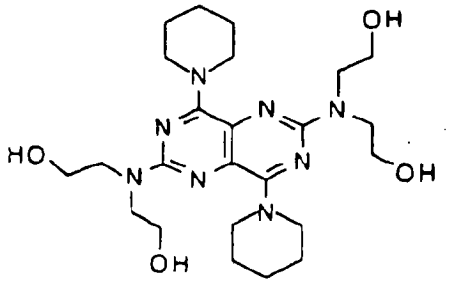
Therefore, the Applicant needs to obtain the pertinent information with the **to-be-marketed Aggrenox ER** formulation. However, this reviewer attempted to comment on the appropriateness of the existing data by deleting, e.g., ~~strikeouts~~, or *adding/clarifying* in ***BOLD*** based on the information submitted in the NDA.

Background Information

AGGRENOX is a combination antiplatelet agent intended for oral administration. Each hard gelatin capsule contains 200 mg dipyridamole in an extended release form and 25 mg aspirin, as an immediate release sugar coated tablet. In addition, each capsule contains the following inactive ingredients: acacia, colloidal silicon dioxide, corn starch, dimethicone, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose phthalate, lactose monohydrate, methacrylic acid copolymer, microcrystalline cellulose, povidone, stearic acid, sucrose, talc, tartaric acid, titanium dioxide, and triacetin.

Dipyridamole

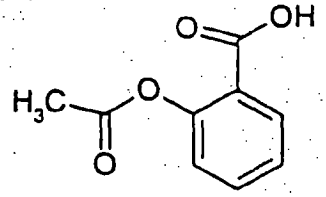
Dipyridamole is an antiplatelet agent chemically described as 2,6-bis(diethanolamino)-4,8-dipiperidino-pyrimido(5,4-d) pyrimidine (= dipyridamole). Dipyridamole is an odorless yellow crystalline substance, having a bitter taste. It is soluble in dilute acids, methanol and chloroform, and is practically insoluble in water. It has the following structural formula:



$C_{24}H_{40}N_8O_4$ Mol. Wt. 504.63

Aspirin

The antiplatelet agent aspirin (acetylsalicylic acid), is chemically known as benzoic acid. Aspirin is an odorless white, needle-like crystalline or powdery substance. When exposed to moisture, aspirin hydrolyzes into salicylic and acetic acids, and gives off a vinegary-odor. It is highly lipid soluble and slightly soluble in water. It has the following structural formula:



$C_9H_8O_4$ Mol. Wt. 180.16

Proposed Labeling:

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

[Reviewer's Comment: As per the reviewing Pharm/Tox Reviewer, Dr. Ke Zhang, this section is acceptable, except, that a sentence, first paragraph, last sentence, has been deleted due to the fact that it is not clear and it was thought that the sentence is not necessary]

Dipyridamole

[Reviewer's Comment: Whether DP is from IR or ER formulations, DP's mechanism of action data can be stand-alone data. Therefore, this section is adequate.]

PHARMACOKINETICS

[General Reviewer's Comment: There are major modifications in this section. The effect of Food section has been taken out completely. The Applicant needs to modify this section with data collected from the pharmacokinetic studies using the To-be-Marketed Aggrenox formulation]

[redacted]

[Reviewer's Comment: This section is not necessary]

DIPYRIDAMOLE

Absorption:

[Reviewer' Comment: Update dissolution data obtained from intact to-be-marketed Aggrenox capsule]

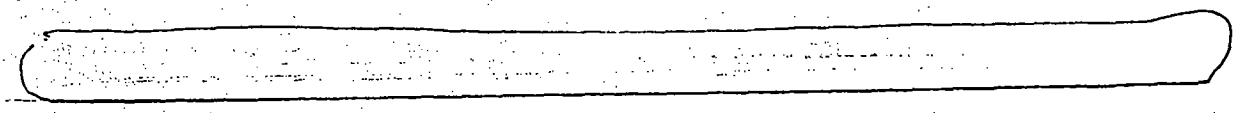
[Reviewer's Comment: % absolute BA - It is not clear if this information is from to-be-marketed Aggrenox formulation; therefore, the sentence has been deleted]

[redacted]

Effect of Food:

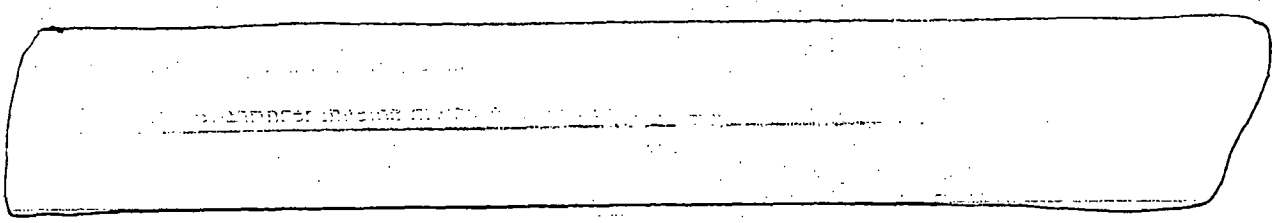
[Reviewer's Comment: Fill in after conducting a food effect study with T-B-Marketed formulation]

[redacted]



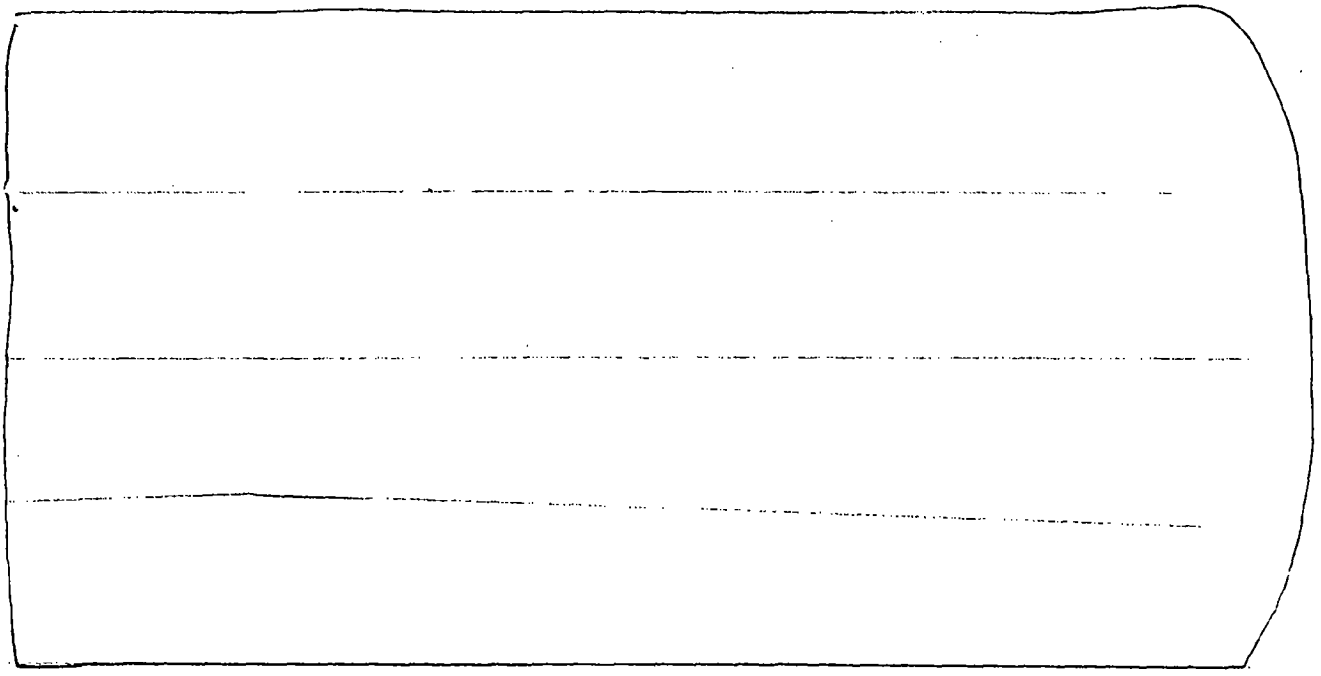
Distribution:

[Reviewer's Comment: Since the Applicant needs to conduct additional PK studies to address deficiencies, the Applicant should re-confirm the Vd]



Metabolism and Elimination:

[Reviewer's Comment: the Applicant should fill-in the metabolites presented in the plasma, and elimination in the urine and feces from the pharmacokinetic studies conducted with the intact to-be-marketed Aggrenox formulation]



Special Populations:

Geriatric Patients:

[Reviewer's Comments: If 'ESPS2 study plasma concentrations' refer to data collected from Population Pharmacokinetic study, the Applicant needs to resubmit the disk. At this time, these sentences will be deleted.]

[Please clarify/identify the study used to support the statement. Identify the formulation used in the study]

Hepatic Dysfunction:

[Reviewer's Comment: There is no study conducted with to-be-marketed Aggrenox formulation in hepatically impaired patients]

[Please clarify/identify the study used to support the statement. Identify the formulation used in the study]

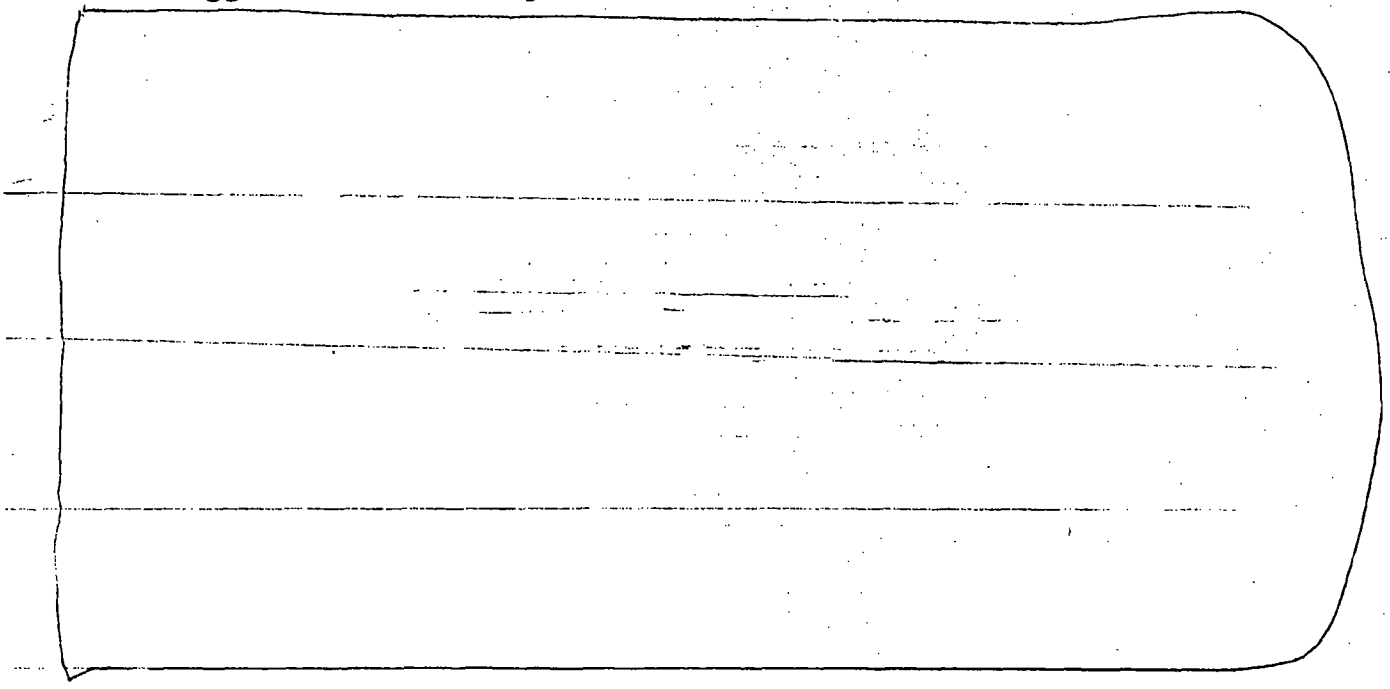
Renal Dysfunction:

[Reviewer's Comment: There is no study conducted with to-be-marketed Aggrenox formulation in renally impaired patients]

[Please clarify/identify the study used to support the statement. Identify the formulation used in the study]

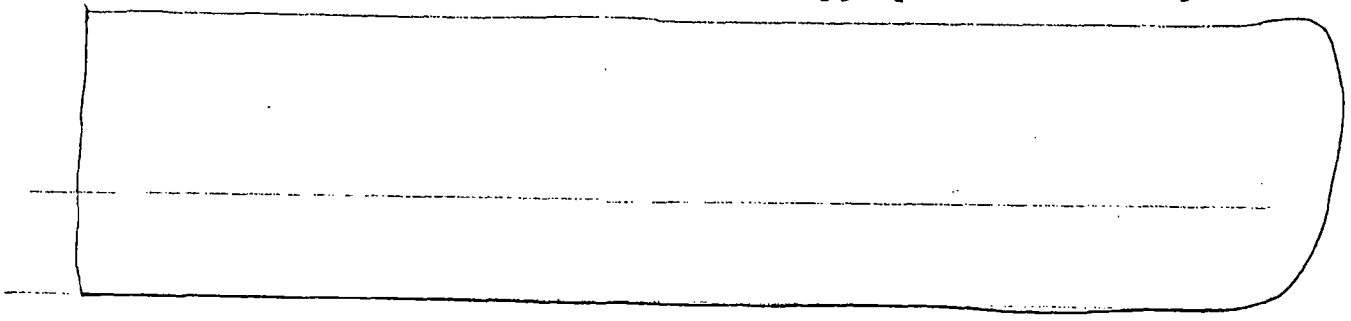
ASPIRIN

[Reviewer's Comment: the Data in this section need to be updated with aspirin data obtained from the intact to-be-marketed Aggrenox formulation]



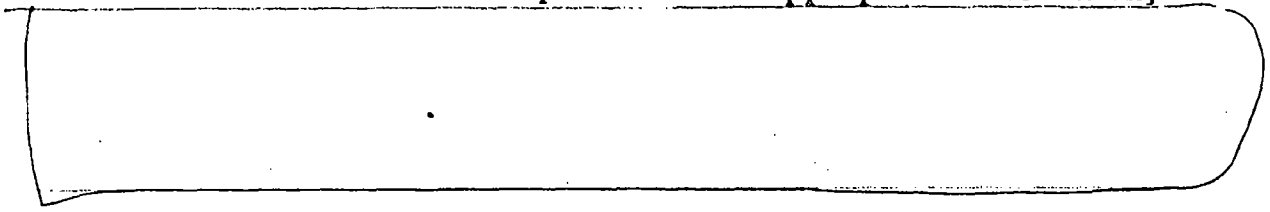
Metabolism:

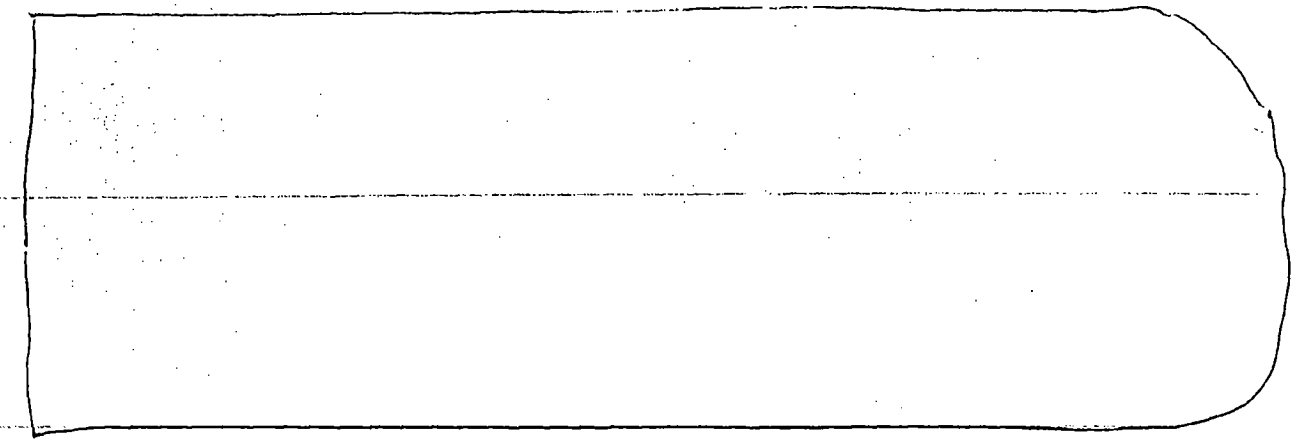
[Reviewer's Comment: Fill in with the appropriate information]



Elimination:

[Reviewer's Comment: Update with the appropriate information]

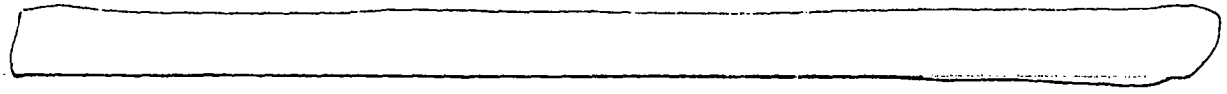




PRECAUTIONS [Note to Sponsor: Please revise most of this section]

[Reviewer's Comment: This reviewer concurs with the recommendation that this section needs major revision]

General



[Note to Sponsor: Include a statement about chest pain, which may be aggravated in patients with and without known underlying coronary artery disease]

[Include a statement about the increased risk of severe bleeding. In ESPS-2 the risk of gastrointestinal and intracranial hemorrhage was higher in the combined treatment group than in the component arms or placebo]

[Include a statement about elevation of liver enzymes and hepatic failure. There is one patient in the Post-Marketing Spontaneous Adverse Reports who developed an elevation of his liver enzymes on Persantin® Retard and died three weeks later of liver failure]

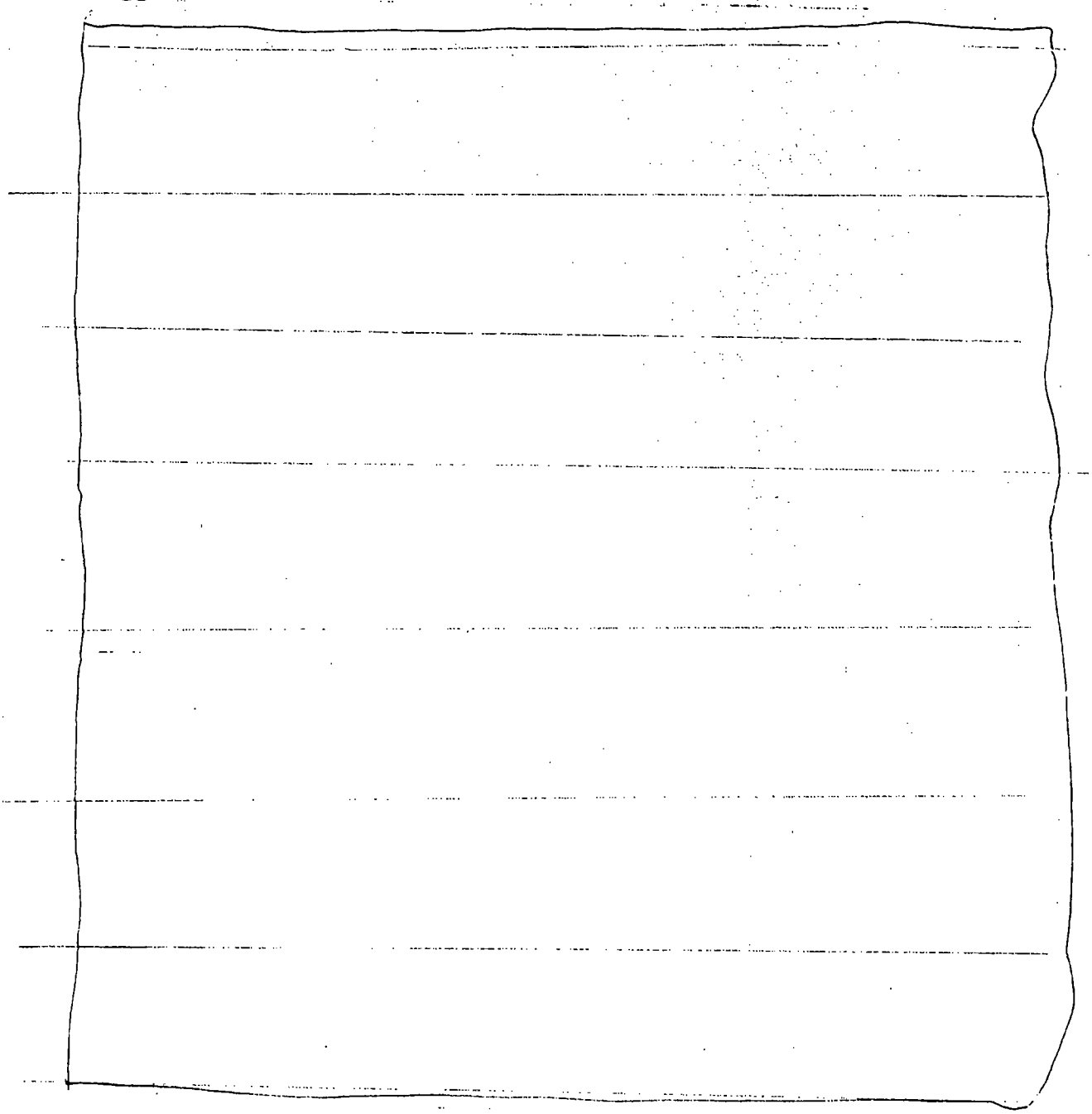
[Include verbatim all of the precautions in the aspirin and dipyridamole labeling]

Drug Interactions

[Reviewer's Comment: It should be stated that there are no pharmacokinetic studies conducted with to-be-marketed Aggrenox formulation to assess drug-drug interactions]

[Note to Sponsor: Update this section with any published reports and literature reviews about drug-drug interactions]

No drug-drug interaction pharmacokinetic studies were conducted with Aggrenox ER formulation.



DOSAGE AND ADMINISTRATION

[Reviewer's Comment: Insert food effect information]

/S/ 6/15/99

APPEARS THIS WAY
ON ORIGINAL

David J. Lee, Ph.D.
Pharmacokineticist, Team Leader
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

Concurrence: /S/ 6/15/99

John Hunt
Deputy Director
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

APPEARS THIS WAY
ON ORIGINAL

DuBeau

JUN 15 1999

Clinical Pharmacology and Biopharmaceutics Review

NDA: 20-884 1P

Title: AGGRENOX™ (extended release dipyridamole 200 mg and immediate release aspirin 25 mg) Capsules.

Reviewer: Alfredo R. Sancho, Ph.D. Serial No.: 000 Submission Date: 12/15/98

Review Date: 6/15/99

Dosage: Oral administration capsules *b.i.d.*

Applicant: Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI)

SYNOPSIS

Aggrenox ER (extended release) is a combination drug product of dipyridamole 200-mg and aspirin 25-mg contained [redacted] Its proposed clinical indication, as stated by the Applicant, is [redacted] The Applicant states that the antithrombotic action of this drug product is the result of the synergistic additive antiplatelet effects of dipyridamole and aspirin.

The Applicant states that the co-administration of dipyridamole (DP) and aspirin (ASA) as separate agents in various dose ratios is a well established clinical practice. The Applicant's proposed drug product, Aggrenox ER, is an alternative fixed dose combination of these two products for patient convenience and compliance. Two other versions of this same combination drug product, 75/330-mg DP/ASA, and 75/50-mg DP/ASA, are already approved and marketed in several other countries.

The Applicant states that Aggrenox ER contains two distinct types of dipyridamole (DP) [redacted]

This NDA submission includes one study with the to-be-marketed formulation (N=1), several studies with varying formulations similar to the to-be-marketed (N=4), and other supporting studies of each of the individual ingredients evaluated separately (N=13). These studies included bioavailability, drug-drug (DP-ASA) interaction, food effect, efficacy/population kinetics, and multiple dose pharmacokinetic profiles.

Most of the PK information is based on DP product formulations alone which may be already approved and marketed in other countries, namely, Persantine ER, Persantine Retard, Persantine Sustained Release, Persantine Modified Release, Persantine Intravenous injection (IV), and Persantine Immediate Release (IR). Only Persantine IR and Persantine IV are approved and marketed in U.S. The approved dose strengths for IR are 25, 50, and 75-mg. The IV approved dose is of 5-mg/ml. There is no detailed information in this submission on how each of these formulations differs in active ingredients and excipients from those formulations already approved by the Agency.

A Phase III clinical pivotal trial was performed in support of the safety and efficacy of this drug product. This pivotal clinical trial is known as "European Stroke Prevention Study 2" or

ESPS2. This study was a multicenter, randomized, parallel group, double blind, placebo controlled, 2 by 2 factorial design study. A total of 6602 patients from 59 centers in 13 European countries received treatment for up to two years. The subjects in ESPS2 received different batches of Aggrenox due to the long treatment period and the limited shelf life of the drug product. The Population Kinetics evaluation provided by the Applicant was performed with 404 patients from the ESPS2 study, which received either Aggrenox or Persantine ER.

The Applicant performed a literature review, of which the criteria and results are presented in this submission. Critical and pertinent information from the provided literature is included in the background sections of this review.

Aggrenox ER is a combination product that contains i) fast and slow extended release dipyridamole pellets (200 mg) and ii) an aspirin tablet (25 mg). Under the Agency's Bioavailability and Bioequivalence Requirements (21 CFR 320.25 (g)), it indicates for a combination product that the purpose of an in vivo bioavailability study is to "determine if the rate and extent of absorption of each active ingredient or therapeutic moiety in the combination drug product is equivalent to the rate and extent of absorption for each active ingredient or therapeutic moiety administered concurrently in separate single-ingredient preparations." The regulations go on to state that, "The reference material in such a bioavailability study should be two or more currently marketed, single-ingredient drug products each of which contains one of the active drug ingredients or therapeutic moieties in the combination drug product". However, the Office of Clinical Pharmacology and Biopharmaceutics feels that such a study may not be necessary for this NDA. The rationale supporting this decision is as follows:

1. The applicant has provided some pharmcokinetic drug-drug interaction data for the two active drug moieties in the combination product, albeit that the to-be-marketed formulation was not studied.

2. Currently there is no FDA approved single-ingredient dipyridamole extended-release capsule formulation that matches the dipyridamole extended-release capsule component of Aggrenox ER that should be administered as a reference in the required study.

3. Patients would not be switched from a single-ingredient dipyridamole product to the to-be-marketed Aggreonox ER product because the only FDA approved product is an immediate-release dosage form that has a different indication than Aggrenox ER.

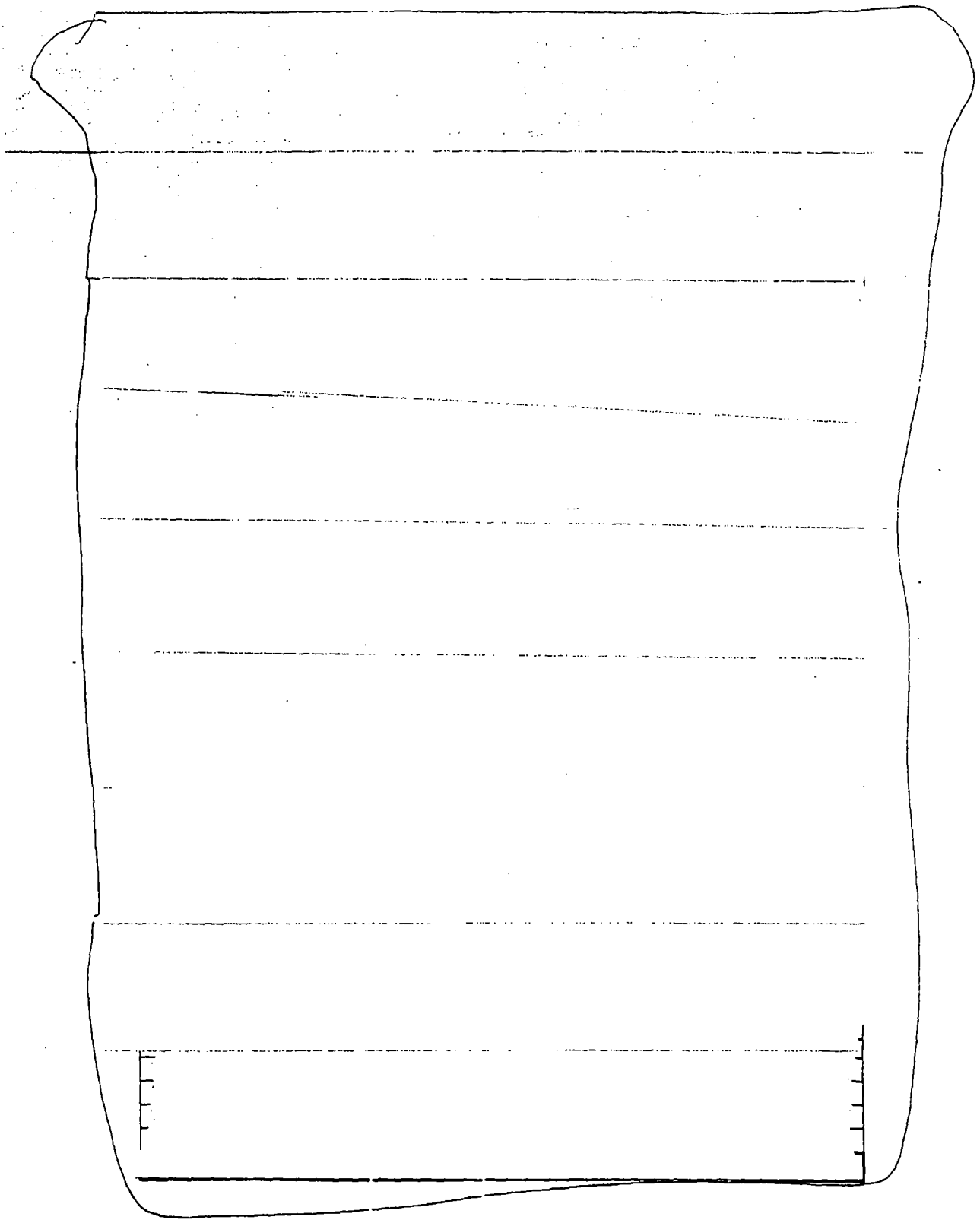
There are items which should be addressed by the applicant since the information and data provided in Section 6 of the NDA does not sufficiently meet the scientific standards and regulatory requirements that are expected under 21 CFR 320. It should be noted that there are important scientific and regulatory issues/deficiencies with this submission as indicated in the "COMMENTS TO THE APPLICANT" section of this review. These comments should be communicated to the firm.

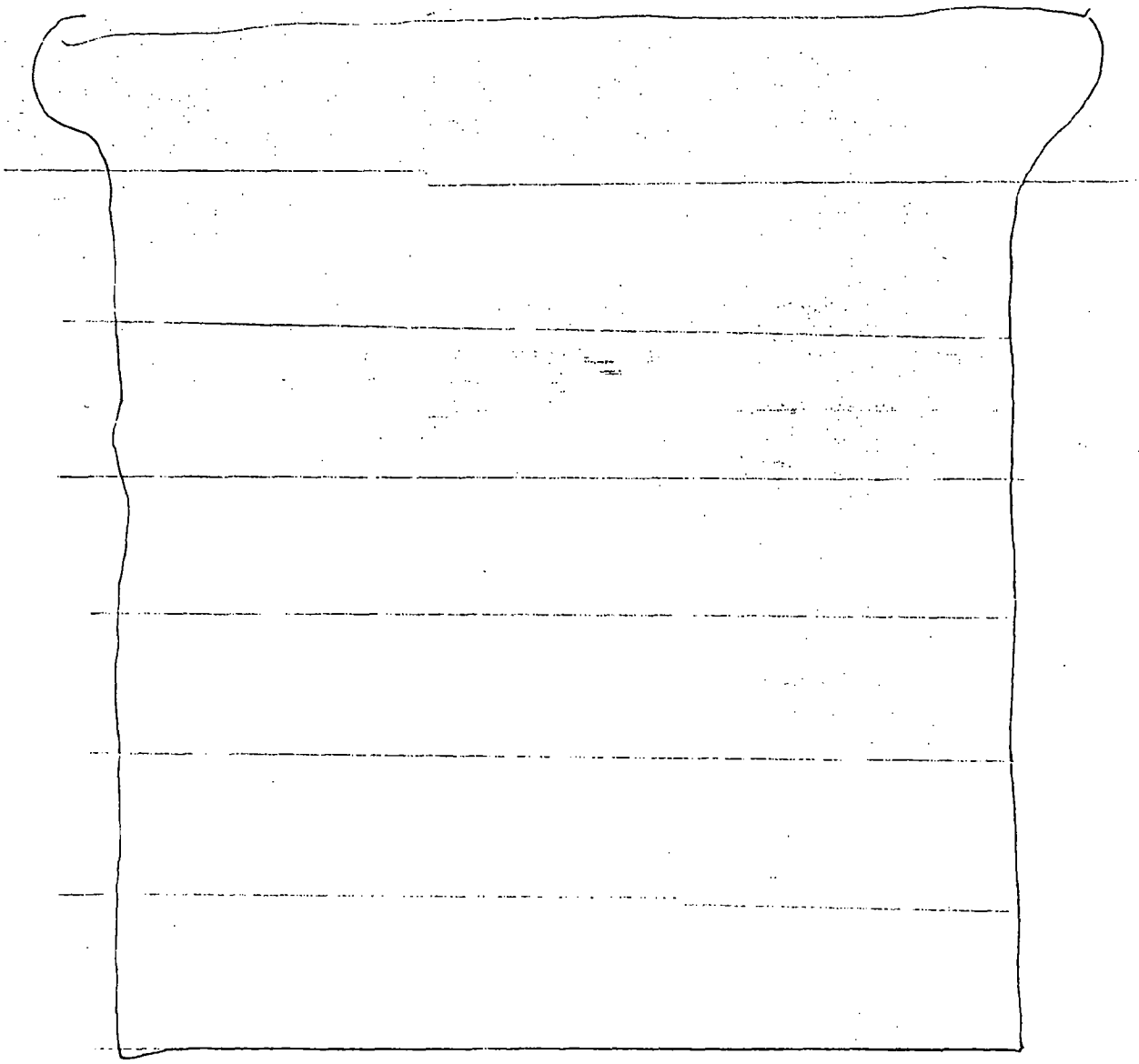
The proposed to-be-marketed formulation of this drug product is as follows:

Ingredients	mg/capsule
ASA	
(ASA)	25.0
Corn Starch	
Colloidal Silicon Dioxide	
Aluminum Stearate	
Lactose Monohydrate	
Microcrystalline cellulose	
Sucrose	
Titanium Dioxide	
Talc	
Water	
Total	
Dipyridamole	200.00
Acacia	
Tartaric Acid	
Hydroxypropyl methylcellulose	
Dimethicone	
Talc	
Povidone	
Methacrylic Acid Copolyme	
Hydroxypropyl methylcellulose Phtahalate	
Triacetin	
Stearic Acid	
Total	
TOTAL CAPSULE WEIGHT	

It should be noted that the components and

to-be-marketed formulation (Chemistry section. 4.0, Table 4.3.1.2:1). In addition, in the same table, the Applicant presented the comparison of DP formulation changes which have been made in 1988, 1993 and proposed to-be-marketed formulation.





BIOLOGICAL BACKGROUND

The Applicant states that they performed a literature review with "Aspirin and/or Antiplatelet Drugs in Patients with TIA or Stroke" as the search criteria. This search provided 35 published reports describing the efficacy findings on whether ASA administration reduces the risk of stroke in patients with a prior TIA or stroke. In these reports, patients received ASA doses ranging from 30 to 1500 mg daily. The Applicant concluded from the reports that it appears that ASA is associated with a reduction in stroke in patients at risk. However, there is no clear and concrete agreement about the dose of ASA necessary to achieve clinical efficacy. The Applicant also states that based on these reports, there is no clear evidence for an ASA dose-response effect on the prevention of secondary ischemic stroke. The Applicant further concludes that the absence of a dose-response relationship support the use of lower rather than higher ASA doses because lower doses of ASA appear to minimize the risk of gastrointestinal side-effects.

From the reports, the antithrombotic effect of DP appears to be due to the following three mechanisms:

1. Stimulation of platelet adenosine receptors as a consequence of the inhibitions of the membrane adenosine carrier by DP ($IC_{50} < 1$ μM).
2. Impairment of the breakdown of cyclic GMP due to inhibition of cGMP phosphodiesterase by DP (IC_{50} human platelet 1.6 μM).
3. Generation of an increased concentration of prostacyclin, due to protection of PGI_2 synthase from oxidative damage by DP (maximal effect at concentrations of about 1 μM).

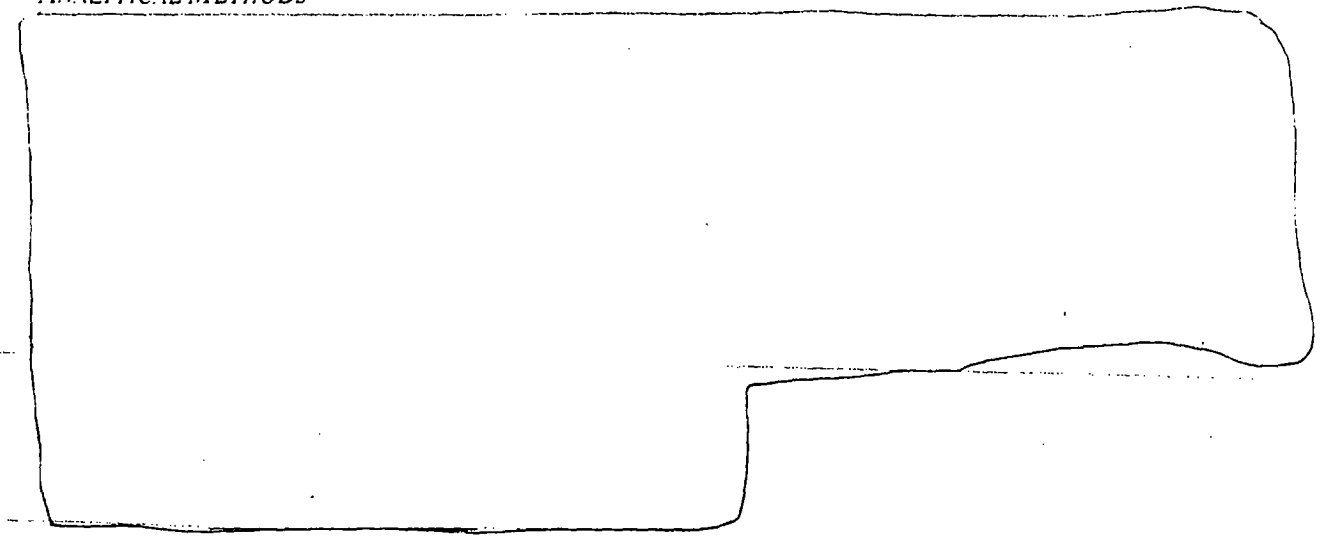
Aspirin acts irreversibly via acetylation of platelet cyclooxygenase, which indicates that its activity is not related to the pharmacokinetics of ASA, but to the life span of the affected platelets, which is approximately 8-10 days. The Applicant proposes a low dose of ASA b.i.d to minimize the possibility of gastrointestinal side effects.

In conclusion, the Applicant states that the antithrombotic action of this drug product is the result of the additive antiplatelet effects of dipyridamole and aspirin. Dipyridamole inhibits the uptake of adenosine into platelets, endothelial cells, and erythrocytes. In addition, the Applicant states that this inhibition is dose dependent, with therapeutic concentrations being between 0.5 and 1.9 μg/ml. Aspirin inhibits platelet aggregation by irreversible inhibition of platelet cyclo-oxygenase and thus inhibits the generation of thromboxane A_2. The exact mechanisms of action are detailed in the submission and package insert of this drug product.

PHARMACOKINETICS

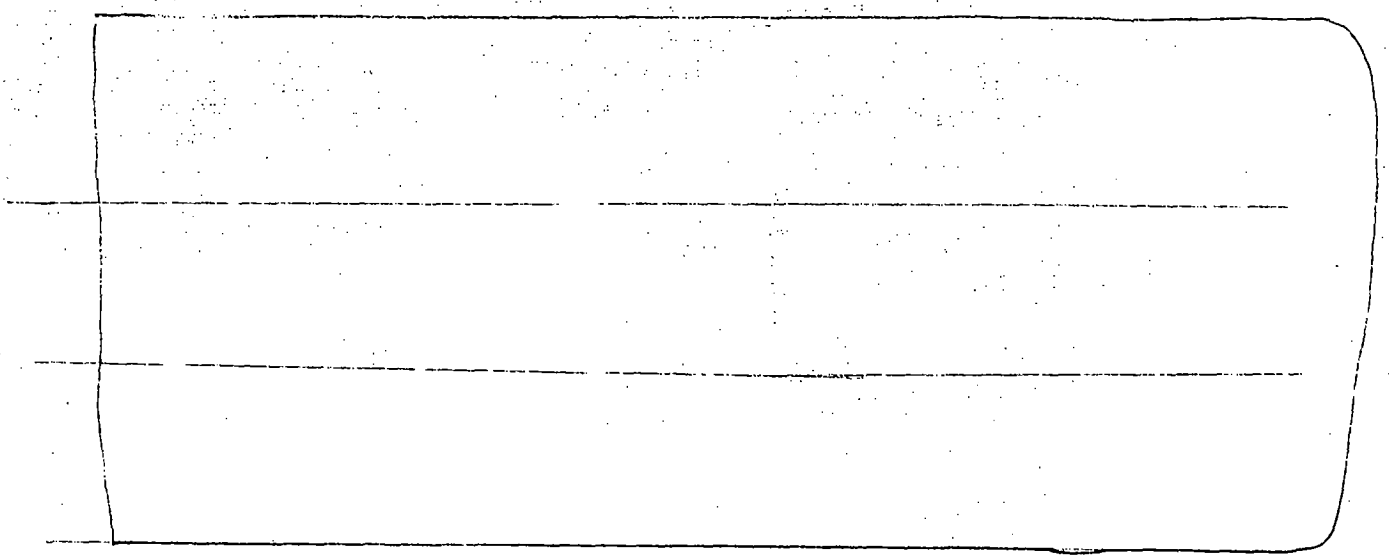
The Applicant states that the pharmacokinetics of the individual components remain unchanged in the proposed combination product. Cmax for DP is reached 2 to 3 hours post administration with steady-state reached within 3 days. DP is heavily metabolized in the liver by conjugation with glucoronic acid to form the monoglucoronide. In plasma, about 80% of the total DP dose exists as the parent compound, while the remaining 20% is monoglucoronide. Excretion of monoglucoride is mainly through the bile, with the renal excretion being minimal (≤ 5%).

ANALYTICAL METHODS



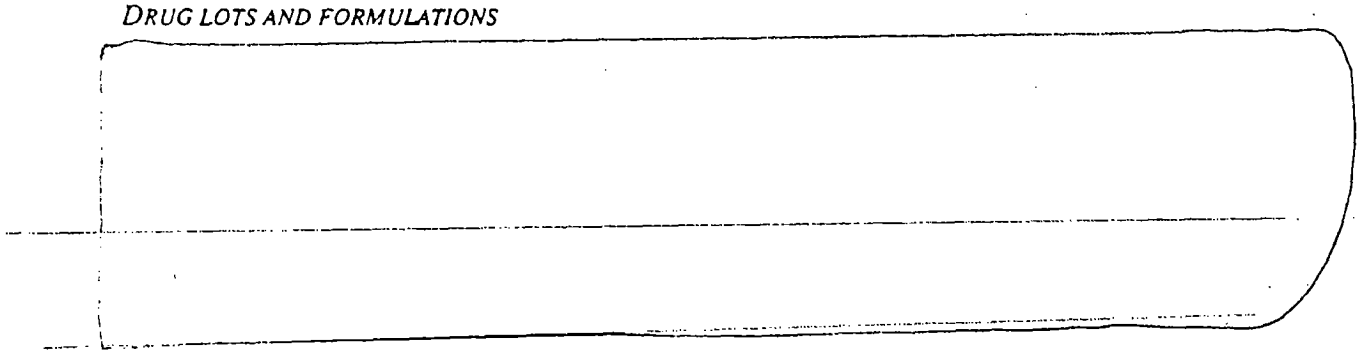
DISSOLUTION

Active Ingredient	
DP	
ASA	



RESULTS

DRUG LOTS AND FORMULATIONS



POPULATION KINETICS RESULTS

The Population Kinetics evaluation provided by the Applicant was performed with 404 patients from the ESPS2 study, which received either Aggrenox or Persantine ER (not approved in U.S.). ESPS2 study was a Phase III clinical pivotal trial performed to support the safety and efficacy of this drug product. This study was a multicenter, randomized, parallel group, double blind, placebo controlled, 2 by 2 factorial design study. A total of 6602 patients from 59 centers in 13 European countries received treatment for up to two years. The subjects in ESPS2 received different batches of Aggrenox due to the long treatment period and the limited shelf life of the drug product. The Applicant states that there was no observed difference between the Aggrenox and Persantine ER treatments, hence this is why they "pooled" their results for the Population Kinetics analysis.

A request for the data and analysis procedure used for the Population Kinetics evaluation was sent to the Applicant. It should be noted that the Applicant has submitted a diskette which can not be read due to unknown reasons. Therefore, no discussion of the results will be presented in this review. Again, this information will be requested from the Applicant in this review.

FOOD EFFECT RESULTS

There is no direct food effect study conducted with the ESPS2 Aggrenox formulations or the to-be marketed formulation. For ASA, there is no study to measure the impact of food on the kinetics of ASA at a dose of 25-mg b.i.d. In the proposed drug product, ASA is of immediate release.

For DP, the Applicant extrapolated the effect of food from the study IP JapFood, which was done with Persantine ER, without ASA. This was a single dose 150-mg study; the Applicant did not describe the content of the meal used in this study. The Applicant states that the Persantine ER dipyridamole [redacted] used were also used in one of the Aggrenox batches used in the ESPS2 study. Furthermore, the Applicant justified the use of Persantine ER in lieu of Aggrenox ER, due to the fact that there is no evidence of drug-drug interaction between ASA and DP. The results of this study are presented in the following table:

JapFood-study with 150-mg Persantine ER without ASA:

Persantine ER				
		Fed	Vs.	Fasted
AUC-	*Mean*	9.46		10.21
µg.hr/ml	*Range*	5.88 – 12.86		6.58 – 13.46
	±SD	1.99		2.63
	Mean Ratio (Test/Ref.)		1.10	
	90% CI		1.01 – 1.15	
		Fed	**Vs.**	**Fasted**
Cmax	*Mean*	1.26		1.67
µg/ml	*Range*	0.89 – 1.86		1.19 – 2.39
	±SD	0.70		0.42
	Mean Ratio (Test/Ref.)		0.99	
	90% CI		**0.78 – 0.94**	
		Fed	**Vs.**	**Fasted**
Tmax	*Mean*	1.92		2.25
Hr	*Range*	1.00 – 3.00		7.43 – 15.07
	±SD	0.66		2.96
	Mean Ratio (Test/Ref.)		0.85	
	90% CI		1.17 – 1.73	

There is a slight reduction in the Cmax of Persantine ER under fed state compared to fasting, 1.26 and 1.67 µg/ml, respectively. The point estimate for Cmax ratio is below 1.0, indicating that the Cmax of fed state is less than that of fasted state and the lower limit is below 0.8 of log-transformed value. The clinical relevance of this may not be significant for the effect of dipyridamole inhibiting the uptake of adenosine into platelets, endothelial cells, and erythrocytes is dose dependent, with therapeutic concentrations being between 0.5 and 1.9 µg/ml.

In addition, the Applicant states that inference for food effect on this drug product can be drawn from the ESPS2 study, because patients were dosed without any restrictions to time of administration or content of meals.

SAFETY

No serious adverse events were mentioned in the reports, except for some GI bleeding. The GI bleeding was observed both in the subjects that received the proposed drug product as well as those receiving placebo, hence it is not considered to be related to the proposed drug product.

BIOEQUIVALENCE

There was only one pertinent bioequivalence study, Study IP 9.123, a multiple-dose study, in which one of the eight different formulations used in the pivotal efficacy trial was compared with the to-be-marketed formulation. The results from this study are presented in the following table (next page, p.12).

The to-be-marketed Aggrenox ER production batch was found to be equivalent to one of the ESPS2 batches, with respect to DP extent of rate and absorption. No significant differences were observed in the pharmacokinetics of SA between the two batches. However, the ASA component of the Aggrenox ER formulation was not equivalent to that of the ESPS2 clinical trial batch with respect to extent of absorption (AUC), or the rate of absorption (Cmax).

With respect to Cmin values (Day 5, prior to morning dose), the following values are obtained from the study: mean ± S.D.

	ESPS2	T-B-Marketed
Cmin µg/ml	0.481 ± 0.146	0.532 ± 0.212

As stated earlier in this document, the Applicant stated that the effect of dipyridamole inhibiting the uptake of adenosine into platelets, endothelial cells, and erythrocytes is dose dependent, with therapeutic concentrations being between 0.5 and 1.9 µg/ml. Therefore, it appears that, on average, Cmin values are above that of the 0.5 µg/ml for the to-be-marketed formulation.

There is another study, IP 21.48, within the "supporting" category that compares two Persantine ER formulations (both of 150-mg b.i.d.) with a Persantine IR formulation (75-mg q.i.d.). The commercial name of the two extended release Persantine formulations is Persantine Retard. There is a formulation difference between these two formulations of Persantine Retard. The Persantine IR 75-mg formulation used as the reference was a tablet. This study and its report have no detailed information on the composition of all tested formulations or how they compare to the to-be-marketed formulation of Aggrenox ER. A request was sent to the Applicant for this information and as of the date of this review, no response has been received.

According to the Applicant, the AUC and Cmax values for the Persantine IR 75-mg tablet were 6.20 µg*h/ml and 1.54 µg/ml, respectively. The AUC and Cmax values for the "newer" formulation of Persantine Retard were 7.05 µg*h/ml and 1.43 µg/ml, respectively. The AUC and Cmax values for the "former" formulation of Persantine Retard were 6.39 µg*h/ml and 1.23 µg/ml, respectively. The reviewer verified none of these values. Nevertheless, using these PK values provided by the Applicant, there is a 14% increase in AUC between the reference product (Persantine IR 75-mg b.i.d.) and the "newer" formulation of Persantine Retard. However, comparison of the reference product with the "former" Persantine Retard formulation, there is only a 3% increase. The rate of absorption (Cmax) for the "newer" Persantine Retard formulation is slightly less than the reference product, and more so for the "former" Persantine Retard formulation. The relevance of these findings to the to-be-marketed formulation of Aggrenox ER can not be established due to the lack of information on the composition of the Persantine Retard formulations used in this study.

1 page
REDACTED
TRADE SECRET/
Confidential
Commercial

DRUG-DRUG INTERACTIONS

Study IP 9.69 was performed to evaluate any drug-drug interaction between the various active ingredients of the proposed combination drug product. Food was given 30 minutes after the administration of Aggrenox ER (i.e., not to-be-marketed formulation or formulation used in ESPS2 study or bioequivalence study) or DP ER formulation. DP, ASA and SA concentrations were compared. The results of this study are presented in the following table, and it appears that there are some drug-drug interaction, i.e., one or both AUC and Cmax values are not equivalent when Aggrenox ER fomulation was compared with DP ER formulation.

For DP comparison, AUC was equivalent between Aggrenox and DP ER formulations. However, the Cmax (0.87-1.46) of the Aggrenox formulation was not equivalent to that of the DP ER formulation; Aggrenox's Cmax was higher than DP ER formulation. For ASA, both AUC and Cmax values were not equivalent; AUC and Cmax for Aggrenox were higher (0.93 – 1.27) and significantly lower (0.59 – 0.84), respectively, than DP ER formulation. For SA, both formulations were equivalent.

The relevance of the observed shorter T_{max} of DP from Aggrenox can not be assessed from this study for there is no detailed safety data (*i.e.*, adverse events) correlated to the pharmacokinetic parameters included in the report. The only adverse events reported in all trial are that of gastrointestinal bleeding, which was reported in subjects receiving, DP, ASA, and PB. The clinical implications of this shorter T_{max} of DP from Aggrenox in conjunction with the observed increases in C_{max} and AUC can not be determined from this study or the data provided.

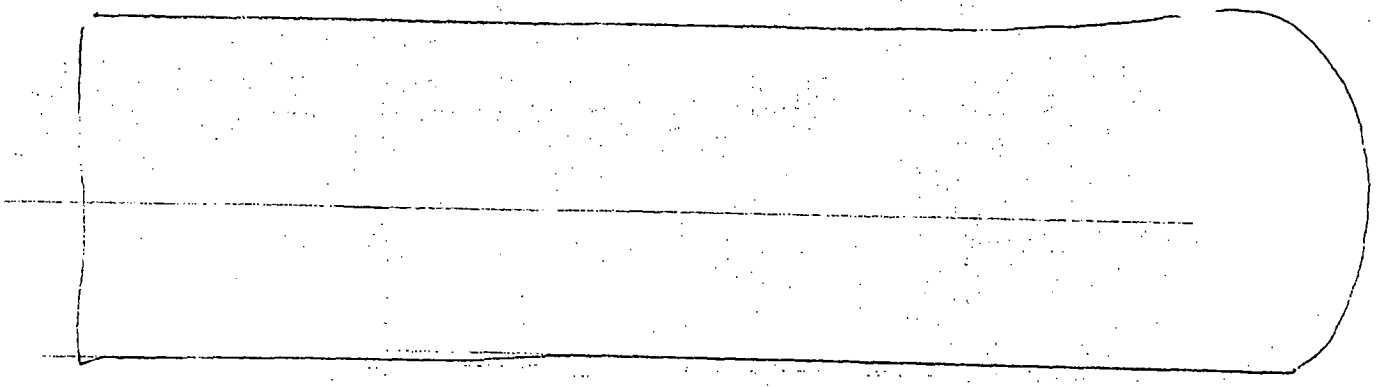
The clinical effect on the anti-platelet activity of ASA, from the delayed rate of absorption of ASA, can not be assessed from this study or the results presented in this report. Since ASA produces its pharmacologic effect via an irreversible acetylation of platelets, the rate of absorption of ASA may not be of major concern.

		DP			ASA			SA		
		Aggrenox ER	Vs.	Persantine ER	Aggrenox ER	Vs.	ASA IR	Aggrenox ER	Vs.	ASA IR
AUC	*Mean*	10.80		9.87	0.31		0.28	4.46		4.49
µg.hr/ml	*Range*	5.93 – 16.1		6.72 – 16.2	0.22 – 0.43		0.21 – 0.38	3.32 – 6.29		3.02 – 6.66
	±SD	3.09		2.62	0.08		0.06	0.96		0.99
Mean Ratio (Test/Ref.)			*1.09*			*1.11*			0.99	
90% CI			*0.97 – 1.21*			*0.93 – 1.27*			0.95 – 1.05	
		Aggrenox	Vs.	DP	Aggrenox	Vs.	ASA	Aggrenox	Vs.	SA
Cmax	*Mean*	2.12		1.84	0.32		0.45	1.51		1.67
µg/ml	*Range*	0.96 – 3.65		1.25 – 3.62	0.18 – 0.46		0.32 – 0.67	1.24 – 2.01		1.27 – 2.13
	±SD	0.83		0.68	0.09		0.10	0.19		0.27
Mean Ratio (Test/Ref.)			*1.15*			*0.71*			0.90	
90% CI			*0.87 – 1.46*			*0.59 – 0.84*			0.85 – 0.97	
		Aggrenox	Vs.	DP	Aggrenox	Vs.	ASA	Aggrenox	Vs.	SA
Tmax	*Mean*	1.79		2.60	0.65		0.54	1.08		0.79
Hr	*Range*	1.25 – 3.00		1.25 – 7.00	0.50 – 1.00		0.25 – 0.75	0.75 – 1.50		0.50 – 1.00
	±SD	0.45		1.57	0.17		0.18	0.25		0.21
Mean Ratio (Test/Ref.)			*0.69*			*1.20*			*1.37*	
90% CI			-			-			-	

APPEARS THIS WAY
ON ORIGINAL

2 Redacted Pages

TRADE Secret / Confidential Commercial



General Comment

Aggrenox ER is a combination product that contains i) fast and slow extended release dipyridamole pellets (200 mg) and ii) an aspirin tablet (25 mg). Under the Agency's Bioavailability and Bioequivalence Requirements (21 CFR 320.25 (g)), it indicates for a combination product that the purpose of an in vivo bioavailability study is to "determine if the rate and extent of absorption of each active ingredient or therapeutic moiety in the combination drug product is equivalent to the rate and extent of absorption for each active ingredient or therapeutic moiety administered concurrently in separate single-ingredient preparations." The regulations go on to state that, "The reference material in such a bioavailability study should be two or more currently marketed, single-ingredient drug products each of which contains one of the active drug ingredients or therapeutic moieties in the combination drug product". Technically such a bioavailablility study for the to-be-marketed Aggrenox ER product was not conducted and submitted in the NDA. However, the Office of Clinical Pharmacology and Biopharmaceutics feels that such a study may not be necessary for this NDA. The rationale supporting this decision is as follows:

1. The applicant has provided some pharmcokinetic drug-drug interaction data for the two active drug moieties in the combination product, albeit that the to-be-marketed formulation was not studied.

2. Currently there is no FDA approved single-ingredient dipyridamole extended-release capsule formulation that matches the dipyridamole extended-release capsule component of Aggrenox ER that should be administered as a reference in the required study.

3. Patients would not be switched from a single-ingredient dipyridamole product to the to-be-marketed Aggreonox ER product because the only FDA approved product is an immediate-release dosage form that has a different indication than Aggrenox ER.

APPEARS THIS WAY
ON ORIGINAL

Comment to Medical Officer

In an attempt to link the to-be-marketed Aggrenox ER formulation (i.e., not studied for safety and efficacy) to one of the eight different "formulations/batches" that was studied in pivotal clinical trial ESPS2, a multiple-dose bioequivalence study, Study #IP 9.123, was conducted. In this study, equivalence was established for AUC and Cmax of dipyridamole and for AUC and Cmax of salicylic acid (a major metabolite of aspirin). For aspirin, the to-be-marketed Aggrenox ER formulation had a greater average Cmax (+28%) and greater average AUC (+11%) than the clinically tested formulation/batch, albeit that the same aspirin tablet formulation was used in both Aggrenox ER capsule batches. The medical officer should assess the importance of the observed differences. For aspirin, the differences are probably not a safety concern knowing that the Aggrenox ER aspirin dose is only 25 mg b.i.d. and OTC aspirin is available in 325 mg tablets and the OTC dose is much greater. Therefore, the increased aspirin systemic exposure would probably only contribute to increased efficacy.

COMMENTS TO THE APPLICANT

The following items should be addressed by the applicant since the information and data provided in Section 6 of the NDA does not sufficiently meet the scientific standards and regulatory requirements that are expected under 21 CFR 320.

1. Bioequivalence issue between the to-be-marketed Aggrenox ER formulation and all clinical trial formulations/batches:

   The to-be-marketed formulation of Aggrenox ER was not used in the pivotal clinical trial ESPS2. Instead, eight different "formulations/batches" of the Aggrenox ER combination product (i.e., related to dipyridamole component) 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). Since the other seven "formulations/batches" were also used to establish the safety and efficacy of this product, a link needs to be established between seven "formulations/batches" and the to-be-marketed Aggrenox ER formulation. Currently the Agency has two Guidances for Industry that address modified release/extended release oral dosage forms as related to differences or changes in formulation, etc. In light of this, for the purpose of comparing the seven other "formulations/batches" used in clinical trial ESPS2 with the to-be-marketed Aggrenox ER formation, information on the composition of the seven other "formulations/batches" should be provided along with the additional in vitro dissolution data as covered under Item # 2 below. Also for all the studied "formulations/batches" (i.e., used in clinical study ESPS2 and Study #IP 9.123), please provide the ratios/percentages of dipyridamole [redacted] per formulation/batch.

2. Dissolution analyses:

Please provide dissolution profile data for dipyridamole for the batch of the to-be-marketed formulation of Aggrenox ER that was used in bioequivalence Study #IP 9.123 using the same dissolution method as described in the NDA submission and used previously for the eight ESPS2 study "formulations/batches". Also provide dissolution profile data on any available production size batches of to-be-marketed Aggrenox ER using the same dissolution method.

3. 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 [redacted] of the to-be-marketed Aggrenox ER formulation, a food effect study should be conducted.

4. To substantiate the extended release claim for the dipyridamole [redacted] component in the Aggrenox ER capsule, information/data should be provided comparing the dipyridamole pharmacokinetics obtained in subjects receiving i) the to-be-marketed Aggrenox ER capsule and ii) the FDA approved immediate release dipyridamole formulation given concurrently with the aspirin tablet that is included in the Aggrenox ER capsule.

5. Please submit a new diskette with the population pharmacokinetic data (e.g., dosing times, drug concentrations, etc.) since the previously provided diskette is not usable.

APPEARS THIS WAY
ON ORIGINAL

RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) has reviewed the NDA 20-884 submitted December 15. 1998. It should be noted that there are important scientific and regulatory issues/deficiencies with this submission as indicated in the "COMMENTS TO THE APPLICANT" section of this review. These comments should be communicated to the firm.

APPEARS THIS WAY
ON ORIGINAL

/S/ 6/15/99

Alfredo R. Sancho, Ph.D.
Clinical Pharmacologist/Pharmacokinetic Reviewer
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

Concurrence:

/S/ 6/15/99

APPEARS THIS WAY
ON ORIGINAL

David Lee, Ph.D.
Team Leader, Pharmacokineticist
Gastrointestinal and Coagulation Section
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

CC: HFD-160 NDA 20-884 (1x); DIV.FILE (1x); DUBEAU (1X); SANCHO (1X); LEE (1X)
HFD-870 JHUNT (1x); MLCHEN (1x)
HFD-850 LESKO
CDR Attn.: Barbara Murphy

APPEARS THIS WAY
ON ORIGINAL