

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

19-979/S-018

Administrative Documents

PATENT INFORMATION FOR SUPPLEMENT TO NDA NO. 19-979

1)	Active Ingredient(s)	Ticlopidine Hydrochloride
2)	Strength(s)	250 mg
3)	Trade Name	Ticlid
4)	Dosage Form and Route of Administration	Tablet, oral
5)	Applicant (Firm) Name	Hoffmann-La Roche Inc.
6)	NDA Supplement Number	Not yet assigned
7A)	First Approval Date of NDA	October 31, 1991
7B)	First Approval Date of Supplemental NDA	Not yet approved
8)	Exclusivity: Date first ANDA could be approved	ANDA for change covered by pending NDA Supplement can not be approved for at least three (3) years from the date pending NDA Supplement is approved
9)	Patent Information	See Attachment

CONFIDENTIAL INFORMATION

*Since the New Drug Application Supplement has not yet been approved, this submission is considered as constituting trade secrets or commercial or financial information which is privileged or confidential within the meaning of the Freedom of Information Act (5 USC 552). It is requested that this submission not be published until the New Drug Application Supplement has been approved.

92371

ATTACHMENT

US Patent Number: 4,591,592

Expiration Date: May 27, 2003

Type of Patent-Indicate all that apply (check applicable boxes):

- 1. Drug Substance (Active Ingredient) Y N
- 2. Drug Product (Composition/Formulation) Y N
- 3. Method of Use Y N

If patent claims method(s) of use, please specify approved uses or uses for which approval is being sought that is covered by patent:

Name of Patent Owner: Syntex (USA) Inc.

US Agent (if patent owner or applicant does not reside or have place of business in the US):

The following declaration statement is required if the above listed patent has Composition/Formulation or Method of Use claims.

The undersigned declares that the above stated United States Patent Number 4,591,592 covers the composition, formulation and/or method of use of Ticlid. This product is:

currently approved under the Federal Food, Drug, and Cosmetic Act.)

OR

the subject of this application for which approval is being sought.)

By: 
 Name: John P. Parise
 Date: December 15, 1999
 Title: Senior Counsel
 Telephone Number: (973) 235-6326

Trade Name TiclidGeneric Name fliclopidineApplicant Name Syntex (U.S.A.)HFD # 110

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 /___/ NO /X/

b) Is it an effectiveness supplement?

YES /X/ NO /___/

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

SE1

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 /___/ NO /X/

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

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 /X/ NO /___/

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

NDA# 19.979 Tidia (ticlopidine)
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 /___/ NO /___/

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

NDA# _____
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 / / 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 / / 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 / / 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 /___/

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:

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.

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"):

STAR'S study _____

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 / X / Explain: To my knowledge, this investigation was not
conducted under an IND. If it was, Syntex was not the
sponsor.

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 / / Explain ! NO / X / Explain Syntex obtained right of reference to these
data from CORDIS, the owner of the STARS claim. Syntex did not
sponsor or provide substantial support for the STARS study.

Investigation #2 !
 YES / / Explain ! NO / / Explain

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA Number: 019979 Trade Name: TICLID (TICLOPIDINE HCL)
Supplement Number: 018 Generic Name: TICLOPIDINE HYDROCHLORIDE
Supplement Type: SE1 Dosage Form:
Regulatory Action: OP COMIS Indication: STROKE PREVENTION
Action Date: 1/24/00

Indication # 1 as adjunctive therapy with aspirin for the prevention of subacute stent thrombosis in patients undergoing successful coronary stent implantation.

Label Adequacy: Does Not Apply

Formulation Needed: NO NEW FORMULATION is needed

Comments (if any): This application was granted a full waiver from the pediatric study requirement on the grounds that the proposed indication is not applicable to the pediatric population/10/19/00-Colleen LoCicero.

Lower Range Upper Range Status Date
0 months 16 years Waived

Comments: This application was granted a full waiver from the pediatric study requirement on the grounds that the proposed indication is not applicable to the pediatric population/10/19/00-Colleen LoCicero.

This page was last edited on 10/19/00

Signature - [Handwritten Signature]

Date 10/19/00

RHPM Review of Draft and Final Printed Labeling
NDA 19-979/SE1-018

Date of draft labeling submission: January 5, 2001
Date draft labeling reviewed: January 11, 2001
Date of final printed labeling submission: March 20, 2001
Date final printed labeling reviewed: April 4, 2001
Product: Ticlid (ticlopidine hydrochloride) Tablets
Sponsor: Syntex (U.S.A.) LLC

Background

The sponsor submitted the January 5, 2001 draft labeling (patient insert and patient package insert) in response to the Agency's November 22, 2000 approvable letter for this supplemental application. The approvable letter requested that the sponsor submit final printed labeling identical to the marked-up draft labeling that accompanied the letter. Draft labeling was submitted, however, as the sponsor revised the labeling that accompanied the approvable letter. As described in the cover letter for the draft labeling submission, changes were made to the new **CLINICAL TRIALS/Stent Patients** subsection and the **BOXED WARNING** section of the package insert. Additionally, editorial changes were made throughout the labeling.

The sponsor notes in the cover letter for the January 5, 2001 draft labeling submission that the labeling template used for this submission is that of the most recently approved labeling (i.e., labeling for S-019, approved June 14, 2000).

Following review of the January 5, 2001 submitted draft labeling and negotiations with the sponsor on the first STARS (Stent Anticoagulation Restenosis Study) table in the **CLINICAL STUDIES/Stent Patients** subsection of the package insert, the Agency requested that the sponsor submit final printed labeling. The final printed labeling is to be identical to the January 5, 2001 submitted draft labeling, with the exception of the first STARS table, which is to be replaced with the table the sponsor sent to the Agency, via facsimile, on February 16, 2001.

Evaluation

January 5, 2001 submitted draft labeling

I reviewed the submitted draft package insert and patient package insert in their entirety. I noted the following differences, which were identified in the submission cover letter, from the last approved labeling (i.e., labeling for S-019, approved June 14, 2000) and the labeling text that accompanied the November 22, 2000 approvable letter.

1. The text "in stroke patients" was added to the first sentence of the fourth paragraph of the **BOXED WARNING**, so that the sentence reads as follows:

Aplastic anemia was not seen during clinical trials in stroke patients, but US physicians reported about 50 cases between 1992 and 1998.

2. The following changes were made to the first table in the **CLINICAL TRIALS/Stent Patients** subsection:
 - a. The heading of the second row was changed from "Stent Thrombosis" to "Primary Endpoint" and numbers (of events) were added to the column entries in this row. These numbers immediately precede the percent values.
 - b. "N" in the "Aspirin" column was changed from 550 to 557.
 - c. The values in the fourth column ("Coumadin + Aspirin"), fourth row ("Q-Wave MI") were changed from 7 (1.3%) to 8 (1.5%).
 - d. The heading for the fifth row was changed from "Subacute Stent Closure" to "Angiographically Evident Thrombosis".
 - e. The percent value in the second column ("TICLID + Aspirin"), last row ("Angiographically Evident Thrombosis") was changed from 0.6 % to 0.5%.
 - f. The values in the fourth column ("Coumadin + Aspirin"), last row ("Angiographically Evident Thrombosis") were changed from 14 (2.6%) to 15 (2.7%).
3. The following changes were made to the second table in the **CLINICAL TRIALS/Stent Patients** subsection:
 - a. The order of the third and fourth columns were switched (i.e., "Aspirin", which was the last column, is now the third column and "Coumadin + Aspirin", which was the third column, is now the last column).
 - b. "N" in the "Aspirin" column was changed from 550 to 557.
 - c. The heading for the fourth row, which was inadvertently left incomplete in the November 22, 2000 approvable letter, was completed. The heading, which read "Neutropenia (\leq ", reads appropriately now "Neutropenia ($\leq 1200/\text{mm}^3$)".
 - d. The number and percent value in the fourth column ("Coumadin + Aspirin"), fourth row ("Neutropenia") were changed from 0 (0%) to 1 (0.2%).

The sponsor noted that the values for the odds ratios and p-values in the tables in the **CLINICAL TRIALS/Stent Patients** subsection would likely need to be corrected to reflect the changes made to these tables.

Additionally, I noted the following changes that were not specifically identified in the submission cover letter:

1. The directions for use (e.g., BID) in the second sentence of the first paragraph of the **CLINICAL TRIALS/Stent Patients** subsection were changed from upper to lower case letters.
2. The text "CLINICAL TRIALS" in the second bullet under the **INDICATIONS AND USAGE** section was no longer bolded.
3. "Table 3." was missing from the heading of the table in the **ADVERSE REACTIONS** section.
4. The word "your" was replaced with the word "the" in the *Why TICLID was Prescribed by Your Doctor/Stent Patients* subsection that was added as the third paragraph of the patient package insert (Patient Leaflet).
5. "Rx only" was added to the end of the package insert, immediately preceding the information on distribution.

Drs. Hung and Throckmorton reviewed the draft labeling submission and found the proposed labeling changes acceptable. Dr. Hung recommended that the sponsor recalculate the odds ratios and p-values for the first table in the **CLINICAL TRIALS/Stent Patients** subsection, based on the changes the sponsor made to this table, and revise these values accordingly. Dr. Throckmorton agreed with this recommendation.

On January 30, 2001, I communicated (via telephone) Dr. Hung's recommendation to the sponsor and on February 16, 2001, the sponsor sent, via facsimile, a revised table. In addition to revising some of the p-values and odds ratios, the sponsor expanded the heading of the row in the table headed "Q-wave MI" to include the text "(Recurrent and Procedure Related)" to provide a more accurate description of these events. Drs. Hung and Throckmorton reviewed the table. Dr. Hung initially recommended several changes. I sent the table, as revised by Dr. Hung, to the sponsor, via facsimile, on February 21, 2001. The sponsor indicated that they would want to discuss with Dr. Hung the changes he proposed. Prior to a conversation with the sponsor, however, Dr. Hung reconsidered the changes he had proposed and decided that the table, as the sponsor proposed in their February 16, 2001 facsimile, was acceptable and did not need to be revised.

Dr. Lipicky stated that, provided Drs. Throckmorton and Hung found the sponsor's changes acceptable, he did not need to review the changes and recommended that I send the proposed labeling to Dr. Temple.

On February 22, 2001, I sent the sponsor's proposed draft labeling, the revised STARS table, and the Division's recommendation to Dr. Temple. Dr. Temple found the proposed labeling and revised table acceptable and suggested that the sponsor submit final printed labeling. I communicated this to the sponsor and on March 20, 2001, the sponsor submitted final printed labeling.

March 20, 2001 submitted final printed labeling

I reviewed the March 20, 2001 submitted final printed labeling (package insert and patient package insert) in its entirety and noted the following differences from the agreed upon labeling text (i.e., the January 5, 2001 submitted draft labeling and February 16, 2001 revised STARS table):

1. The order of the STARS title and acronym in the first sentence in the first paragraph of the **CLINICAL TRIALS/*Stent Patients*** subsection was changed from the following:

[

]

to the following:

(Stent Anticoagulation Restenosis Study or STARS)

2. A closing parenthesis was added appropriately to follow "qd" in the second sentence in the first paragraph of the **CLINICAL TRIALS/*Stent Patients*** subsection.
3. The word "four" was replaced with the numeral "4" in the first sentence in the second paragraph of the **CLINICAL TRIALS/*Stent Patients*** subsection.

Recommendation

Although the submitted final printed labeling deviates from the agreed upon labeling text, the changes are minor and editorial in nature and are therefore acceptable. I will prepare an approval on draft labeling letter for Dr. Temple's signature.

/S/

Colleen LoCicero, RHPM

RHPM Review of Draft Labeling
NDA 19-979/SE1-018

Date labeling submitted: January 20, 2000
Date labeling reviewed: June 28, 2000
Date review finalized: November 2, 2000
Product: Ticlid (ticlopidine hydrochloride) Tablets
Sponsor: Syntex (U.S.A.) Inc.

Background

This supplemental application proposes a new indication for Ticlid as adjunctive therapy with aspirin in the prevention of subacute stent thrombosis in patients undergoing successful coronary stent implantation. In support of the proposed indication, the submission includes safety and efficacy data derived from a comprehensive review of the medical literature and authorization from Cordis for the Agency to access the STARS (Stent Anticoagulation Restenosis Study) data on behalf of Syntex. Additionally, the submission contains labeling revised to include information relevant to the proposed indication.

Evaluation

I reviewed the submitted draft package insert and patient package insert in their entirety and noted the following changes from the approved labeling:

1. The text "in stroke patients" has been added to the first sentence of the second paragraph in the BOXED WARNING at the beginning of the package insert as follows:

***Neutropenia/Agranulocytosis:* Among 2048 patients in clinical trials in stroke patients, there were 50 cases (2.4%) of neutropenia (less than 1200 neutrophils/mm³), and the neutrophil count was below 450/mm³ in 17 of these patients (0.8% of the total population).**

2. The text "in stroke patients" has been added to the first sentence of the third paragraph in the BOXED WARNING at the beginning of the package insert as follows:

***TTP:* One case of thrombotic thrombocytopenic purpura was reported during clinical trials in stroke patients.**

3. The heading *Stroke Patients* has been added to the first sentence of the CLINICAL TRIALS section, as follows:

6 pages redacted from this section of
the approval package consisted of draft labeling

To his November 2, 2000 memorandum concerning this application, Dr. Lipicky appended his suggestions regarding the sponsor's proposed revised labeling. He recommends revising the **CLINICAL STUDIES/Stent Patients** subsection that was added to the package insert. He concludes that the changes made to the **INDICATIONS** and **DOSAGE AND ADMINISTRATION** sections are acceptable.

Conclusion

The labeling revisions are limited to the addition and deletion of text and tables that include information relevant to the new indication. The acceptability of the proposed labeling revisions will depend on the action the Agency decides to take on this application and any internal labeling discussions and/or negotiations with the sponsor that ensue:

/s/

11/13/00

Colleen LoCicero, RHPM

cc: NDA 19-979/S-018
HFD-110
HFD-110/Blount
HFD-110/LoCicero

RHPM Package Overview

Date: November 2, 2000

Application: NDA 19-979/SE1-018
Ticlid (ticlopidine hydrochloride) Tablets

Applicant: Syntex (U.S.A.) Inc.

Classification: 6S

User Fee Goal: November 24, 2000 (primary)
January 24, 2001 (secondary)

Background

This supplemental application proposes a new indication for Ticlid as adjunctive therapy with aspirin for the subacute stent thrombosis in patients undergoing successful coronary stent implantation. The application contains data from published literature and a right of reference to the STARS (Stent Anticoagulation Restenosis Study) data to support the proposed indication.

Because of Agency concerns with the considerable off-label use of ticlopidine in the prevention of subacute stent thrombosis, the Agency and sponsor discussed the use of ticlopidine in this setting on several occasions prior to the submission of this application. During a meeting on April 29, 1998, the sponsor asked the Agency what would be needed to support a supplement for an indication in this setting. In this and subsequent meetings and teleconferences on this subject, the Agency stated that both the STARS and ISAR (Intracoronary Stenting and Antithrombotic Regimen Trial) data would be needed to support a supplement for an indication in this setting.

The sponsor was successful in obtaining a right of reference to the STARS data, but was unsuccessful in obtaining the ISAR data (or right of reference to the data), although they reportedly made several attempts to do so. Because there was a public health concern with the considerable off-label use of ticlopidine in this setting and no approved alternative drug therapy, the Division agreed to contact the ISAR primary investigator to request the ISAR data on behalf of Syntex. Syntex submitted this application with a right of reference to the STARS data only and data from published literature to support the proposed indication. Shortly after receiving this application, the Division attempted several times to contact the ISAR study primary investigator to request the ISAR data, but was not successful.

Labeling

The sponsor has provided draft revised labeling (package insert and patient package insert). A review of the sponsor's proposed labeling is attached to this overview. Dr. Lipicky has revised the **CLINICAL TRIALS/Stent Patients** subsection that was added to the package insert. He finds the proposed changes to the **INDICATIONS** and **DOSAGE AND ADMINISTRATION** sections to be acceptable. His labeling suggestions are attached to his memorandum.

Exclusivity

Because the sponsor does not own the data that support this application, they did not request and are not entitled to exclusivity for the proposed indication.

Pediatric Rule

The sponsor requested and was granted a waiver from the pediatric study requirement for this application, based on the grounds that the proposed indication is not applicable to the pediatric population.

Financial Disclosure/Debarment Certification

The original application did not include financial disclosure information or debarment certification for the Stent Anticoagulation Restenosis Study (STARS). On March 27, 2000, the sponsor submitted to the application copies of three facsimiles they had sent to Ms. Linda Carter describing their attempts to obtain financial disclosure information and debarment certification from the STARS sponsor. In a March 24, 2000 e-mail message and again in a March 29, 2000 conversation, Ms. Carter indicated that the sponsor demonstrated due diligence in attempting to obtain this information and therefore adequately addressed the financial disclosure and debarment certification requirements.

DSI

Because Dr. Hung concluded that the STARS results were not dependent on any one site and that elimination of any one site would not appreciably change the study outcome, the Division did not request a DSI audit of STARS.

Chemistry

No chemistry was included in this application. Dr. Zielinski evaluated the need for an environmental assessment, in accordance with 21 CFR 25.20 (l), and concluded that this application meets the criteria for categorical exclusion from the requirement to prepare an Environmental Assessment as described under 21 CFR 25.31 (b).

Statistical

In his September 13, 2000 review of this application, Dr. Hung concludes that he is uncertain as to whether the results of the four trials integrated meet the usual standard in terms of strength of statistical evidence normally required for a well-controlled trial.

Primary Medical

Dr. Throckmorton

In his October 11, 2000 review of this application, Dr. Throckmorton recommends approval of this application, although he notes that this recommendation is based on two imperfect datasets.

Dr. Fredd

Dr. Fredd's October 15, 1998 consult to CDRH of a review of the STARS data is included in this package. In his review, Dr. Fredd concludes that the STARS data, supported by the ISAR data, provide evidence to support efficacy of ticlopidine to prevent stent thrombosis. He notes that aspirin and heparin are adjunctive therapy in this context. He adds that the adverse reaction data and pharmacology of ticlopidine might support limiting use to no more than two weeks.

Secondary Medical

In his November 2, 2000 memorandum concerning this application, Dr. Lipicky concludes that the application is not approvable, but he adds that it is a close call. He notes that most of the supporting studies are open-label and believes the need for revascularization, an endpoint the Agency typically considers "soft", drives most of the outcomes. He states that this is not a database he would like to have setting a precedent.

Dr. Lipicky's labeling suggestions are attached to his memorandum.

Safety Update

A safety update was not submitted for this application, as the studies submitted to support this application have been completed for some time. There are, therefore, no new safety data from these studies to review.

RHPM Summary

All primary and secondary reviews are completed. To my knowledge, there are no outstanding issues that would preclude taking an action on this application. Both an approvable and not approvable letter will be sent to Dr. Temple.

/S/

11/13/00

Colleen LoCicero, RHPM

cc: NDA 19-979/S-018
HFD-110
HFD-110/Blount
HFD-110/LoCicero

MEMORANDUM

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

DATE: November 28, 2000

FROM: Director, Office of Drug Evaluation I, HFD-101

SUBJECT: Ticlopidine-stents; NDA 19-979/SE1-018, Hoffmann-La Roche

TO: Director, Division of Cardio-Renal Drug Products, HFD-110

I have examined your memorandum and reviews of Drs. Throckmorton, Fredd and Hung. This has obviously been a difficult review for everyone, the principal problems being the unblinded nature of all the trials together with a possibly subjective endpoint, and the unavailability of back-up data for all the trials but STARS. There is, however, great consistency in the reported effect of ticlopidine on the death/MI/subacute closure endpoint, as well as its components (other than death), and the risk reduction is sizable. The results in STARS, where we do have data access, are impressive both with respect to effect size and level of statistical significance. There are 2 data sets (STARS and a metaanalysis of 4 studies) that show consistent results directionally and, in most respects statistically as well, even if 4/5 lack detailed data (Table 1) and even if the planned endpoints were somewhat different (Table 2).

I should note that in STARS I believe the most relevant comparison is aspirin and ticlopidine vs. aspirin, not vs. aspirin plus coumadin. I believe the pooled comparator in STARS represents an interesting and conservative analysis, especially if the intended primary analysis is ambiguous, but Dr. Fredd indicates that FDA's "primary" analysis was always the T&A vs. A analysis. On this analysis, the STARS result is very strong (OR 0.14, $p=0.001$), less than the level we generally consider needed to base a conclusion on a single controlled trial. With respect to the subjective nature of the decision to carry out a procedure, although decisions to perform CABG and angioplasty have subjective elements, in STARS the required angiographic documentation of thrombotic occlusion at the time of urgent angioplasty seems to render the endpoint reasonably objective.

APPEARS THIS WAY
ON ORIGINAL

Table 1
Results from Trials of Ticlopidine After Coronary Stent Placement^a.

Trial/ Endpoint	ASA	ASA +Ticlopidine	ASA +Coumadin	Odds Ratio (95% C.I.), p-Value A+T vs. A ^b	Odds Ratio (95% C.I.), p-Value A+T vs. A+C ^b
STAR Study (STARS)	N=557	N=546	N=550		
STARS Primary Endpoint (‘Stent Thrombosis’ at 30 days) ^c	21 (3.8%)	3 (0.6%)	14 (2.6%)	0.14 (0.04, 0.048), 0.001	0.21 (0.06, 0.74), p=0.008
Death	1 (0.2%)	0 (0%)	0 (0%)	--	--
Q-Wave MI	12 (2.2%)	1 (0.2%)	7 (1.3%)	0.08 (0.01, 0.64), 0.003	0.14 (0.02, 1.16), 0.069
NQWMI	33 (5.9%)	35 (6.4%)	41 (7.5%)	1.1 (0.67, 1.78), 0.74	0.85 (0.53, 1.36), 0.50
Sub-acute Stent Closure^d	16 (2.9%)	3 (0.6%)	14 (2.6%)	0.19 (0.05, 0.64), 0.004	0.21 (0.06, 0.74), 0.012
Death, All MIs, Sub-acute Stent Closure	50 (9.0%)	37 (6.8%)	54 (9.8%)	0.74 (0.47, 1.15), 0.18	0.67 (0.43, 1.03), 0.069
Death, All MIs	46 (8.3%)	36 (6.6%)	48 (8.7%)	0.78 (0.49, 1.24), 0.39	0.74 (0.47, 1.16) 0.29
Death, Q-Wave MI	13 (2.3%)	1 (0.2%)	7 (1.3%)	0.08 (0.01, 0.60), 0.002	0.14 (0.02, 1.16), 0.069

a. Data from individual FDA reviews, published papers of trials, and NDA 19-979 serial 018 (submitted 1.20.99).

b. A= ASA. T= Ticlopidine, C= Coumadin and coumadin-like drugs.

c. Death, Q-wave MI, Urgent Revascularization.

d. Sub-acute Stent Thrombosis defined as angiographic thrombus within the stented vessel demonstrated at the time of documented ischemia (chest pain and ECG changes) requiring emergent revascularization.

Results from Trials of Ticlopidine After Coronary Stent Placement (cont)^a.

Trial/ Endpoint	ASA	ASA +Ticlopidine	ASA +Coumadin	Odds Ratio (95% C.I.), p-Value A+T vs. A ^b	Odds Ratio (95% C.I.), p-Value A+T vs. A+C ^b
FANTASTIC Trial^c		N=243	N=230		
Death		2 (0.8%)	4 (1.7%)		0.47 (0.09, 2.58), 0.37
Q-Wave MI		3 (1.2%)	6 (2.6%)		0.47 (0.12, 1.88), 0.27
Non-Q-Wave MI		9 (3.7%)	9 (3.9%)		0.94 (0.37, 2.42), 0.9
Subacute Stent Thrombosis ^d		1 (0.4%)	8 (3.5%)		0.1 (0.01, 0.92), 0.01
Death/MI		14 (5.8%)	19 (8.3%)		0.68 (0.33, 1.39), 0.29
Hall et al^e	N=103	N=123			
Death	3 (2.9%)	0 (0%)		0.14 (0.01, 2.74), 0.10	
MI	4 (3.9%)	1 (0.8%)		0.20 (0.02, 1.84), 0.10	
Death/MI	4 (3.9%)	1 (0.8%)		0.20 (0.02, 1.84), 0.10	
Stent Thrombosis ^f	3 (2.9%)	1 (0.8%)		0.27 (0.03, 2.67), 0.20	
ISAR Study^g		N=257	N=260		
Primary Endpoint: Death, MI, CABG, Repeat PTCA ^h		4 (1.6%)	16 (6.2%)		0.24 (0.08, 0.73), 0.01
Death		1 (0.4%)	2 (0.8%)		0.50 (0.05, 5.59), 1.0
MI (Q-Wave and NQWMI)		2 (0.8%)	11 (4.2%)		0.18 (0.04, 0.81), 0.02
Stent Thrombosis ⁱ		2 (0.8%)	14 (5.4%)		0.14 (0.03, 0.61), 0.004
Death/MI		3 (1.2%)	11 (4.2%)		0.27 (0.07, 0.97), 0.032
MATTIS Study^h		N=177	N=173		
Primary Endpoint: Death, MI, CABG, Repeat PTCA		10 (5.6%)	19 (11.0%)		0.49 (0.22, 1.08), 0.07
Death		3 (1.7%)	2 (1.2%)		1.47 (0.24, 8.93), 0.67
MI		6 (3.4%)	12 (6.9%)		0.47 (0.17, 1.28), 0.14
Death/MI		9 (5.1%)	13 (7.5%)		0.66 (0.27, 1.58), 0.35
Meta-Analysisⁱ	N=103^j	N=799	N=663		
Death/MI	See j	26 (3.3%)	43 (6.5%)		0.48 (0.29, 0.80), 0.004
Death/MI/CABG	See j	29/800 (3.6%)	See k		See k

a. Data from individual FDA reviews, published papers of trials, and NDA 19-979 serial 018 (submitted 1.20.99).

b. A= ASA. T= Ticlopidine, C= Coumadin and coumadin-like drugs.

d. Sub-acute Stent Thrombosis defined as angiographic thrombus within the stented vessel demonstrated at the time of documented ischemia (chest pain and ECG changes) requiring emergent revascularization.

e. Primary endpoint of the FANTASTIC trial was bleeding events. Definition of subacute stent thrombosis different from that use in STARS: 'stent occlusion occurring >24 hours after stent implantation.' In the absence of angiographic confirmation, the ECG nad cardiac enzyme criteria for MI were used.

f. Primary endpoints of Hall et al study (no primary stated): stent thrombosis, death, MI, need for CABG/ repeat angioplasty, and 'significant medication side effects requiring termination of the medication.' Definition of stent thrombosis different from STARS: angiographically documented occlusions with TIMI grade 0 flow at stent site >24 hours after procedure.

g. Primary endpoint of ISAR study: death, MI, CABG, repeat PCI. Stent thrombosis not defined paper, but angiographic occlusion of the target vessel was a secondary endpoint.

h. Primary endpoint in MATTIS: cardiovascular death, MI in territory of stent, repeat PCI or CABG. Stent thrombosis was not used as an endpoint in MATTIS.

i. Integrated analysis of the four randomized trials FANTASTIC, ISAR, Hall et al, and MATTIS.

j. The only study that studied ASA alone was Hall et al.

k. FANTASTIC did not collect data on this endpoint.

Table 2
Endpoints from the Five Randomized Trials of Ticlopidine^b.

Trial	Endpoint	Timing of Endpoint
STARS	Death, Q-Wave MI, and angiographic thrombus within the stented vessel demonstrated at the time of documented ischemia (chest pain and ECG changes) requiring emergent revascularization	30 Days
FANTASTIC	Bleeding events	45 Days
Hall et al	No specified primary endpoint: stent thrombosis, death, MI, need for CABG/ repeat angioplasty, and 'significant medication side effects requiring termination of the medication all measured.	30 Days
ISAR	Death, MI, CABG, repeat PCI ^a	30 Days
MATTIS	Cardiovascular death, MI in territory of stent, repeat PCI or CABG	30 Days

a. PCI= percutaneous coronary intervention.

b. Data from publications and from Steve Fredd's review of STARS.

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ON ORIGINAL

The STARS result is much weaker if NQWMI's are counted, but the NQWMI's were apparently in many cases early (pre-T) and were mainly small enzyme elevations. The failure to see an effect on them does not undermine the results on the planned endpoint.

Conclusion

STARS and 4 other randomized studies support the effectiveness of ticlopidine in reducing the risk of stent thrombosis (defined in STARS as death, QWMI, and documented stent occlusion requiring urgent intervention). Results are very consistent over 2 large and 3 small studies for the combined endpoint, even when compared with aspirin plus anticoagulation, and the risk reduction is substantial. Lack of blinding should not greatly affect most endpoint assessments (re-doing a stent takes a lot of thought and effort and is not done frivolously). I believe this supplement is approvable.

1st
v Robert Temple, M.D.

cc:

Orig.NDA 19-979/S-018

HFD-110

HFD-110/C Locicero

HFD-101/R Temple

draft:sb/11/21/00

final:sb/11/28/00

Food and Drug Administration
Rockville MD 20857

FEB 9 2000

Albert Schömig, M.D.
The I. Medizinische Klinik der Technischen Universität München
Klinikum rechts der ISAR
Ismaninger Strasse 22
81675 Munich, Germany

Dear Dr. Schömig:

This letter is in reference to your recent work comparing antiplatelet and anticoagulant therapies after coronary-artery stent placement (the ISAR trial). Recently, the Food and Drug Administration (FDA) has been asked to review antiplatelet and anticoagulant drug use after coronary-artery stenting. We are familiar with the published results of your trial as they appeared in the *New England Journal of Medicine* in 1996¹. However, additional information might be gained from analysis of the primary data that would aid us in our review. Bearing in mind the strict confidentiality of all data submitted to the FDA, we would be interested in discussing how to obtain access to those primary data with you. Please contact us at your earliest convenience regarding this matter. Our address and telephone number are as follows:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products
Attention: Document Control Room, HFD-110
5600 Fishers Lane
Rockville, MD 20857
(301) 594-5364

Thank you for your attention to this matter.

Sincerely yours,



Raymond Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

1. A Randomized Comparison of Antiplatelet and Anticoagulant Therapy after the Placement of Coronary-Artery Stents. Schomig, A., Neumann, F.-J., Kastrati, A., Schuhlen, H., Blasini, R., Hadamitzky, M., Walter, H., Zitzmann-Roth, E.-M., Richardt, G., Alt, E., Schmitt, C., and Ulm, K.

Minutes of a teleconference

Date of teleconference: April 14, 1999
Product: Ticlid (ticlopidine) Tablet
NDA 19-979
Sponsor: Hoffmann-LaRoche, Inc.
Purpose: discuss agenda for April 20 meeting and what would be needed for a stent indication
Teleconference Chair: Robert Fenichel, M.D., Ph.D.
Teleconference Recorder: Colleen LoCicero
Participants:

FDA

Robert Fenichel, M.D., Ph.D. Deputy Director, Division of Cardio-Renal Drug Products (HFD-110)
Douglas Throckmorton, M.D. Medical Officer, HFD-110
Colleen LoCicero Consumer Safety Officer, HFD-110

Hoffmann-LaRoche, Inc.

Dr. Kim Thacker Medical Director, Roche Laboratories
Dr. Attila Kursun Medical Director, Roche Laboratories
Dr. Dionigi Maladorno Director, Drug Safety
Mr. Al Masucci Project Leader, Marketing
Ms. Peggy Jack Program Director, Drug Regulatory Affairs
Ms. Lynn DeVenezia-Tobias Program Manager, Drug Regulatory Affairs

Background

The sponsor requested this teleconference with the Agency to discuss the agenda for the April 22 meeting and what the Agency would expect in a submission for a stent indication.

The teleconference

Discussion Point #1: April 22 meeting

At the April 22 meeting, Roche plans to update the Agency on their preparations for a possible July Advisory Committee Meeting. They plan to present the position they will most likely take at the Advisory Committee Meeting with regards to Ticlid in stroke

prevention. They also plan to discuss and hope to have available some of the preliminary results from their risk-benefit analysis. The Agency noted that a formal presentation will not be necessary, as next week's meeting is intended to be an informal discussion of the Ticlid issues.

Discussion Point #2: Ticlid's patient populations

In our recent discussions about Ticlid, the Agency has identified three patient populations for Ticlid. These patient populations are as follows:

- a) patients presenting with a new increased risk of stroke
- b) patients with an increased risk of stroke who have been taking Ticlid for more than three months without experiencing any hematologic toxicity.
- c) stent patients.

The question to consider for the first group is under what circumstances should Ticlid be prescribed for these patients, and if such circumstances exist, what precautions should be taken with regards to the hematologic toxicity.

The risk of hematologic toxicity for the second group is slight. They probably do not need additional precautions, beyond those they are currently taking, to safely continue on Ticlid therapy.

Although the third group is prescribed Ticlid for an indication for which it is not currently approved we must consider this population as we believe it might constitute the majority of Ticlid patients.

It might be that it will be necessary to treat each population differently with respect to the availability of Ticlid and how it will be prescribed and administered.

Discussion Point #3: Ticlid data sets

Roche has located the TASS and CATS data sets and should have access to these data in early May. Roche agreed to provide the Agency with copies of these data sets.

Discussion Point #4: First-line versus second-line status

In the current labeling, Ticlid is designated second-line therapy to aspirin. According to the labeling, therefore, Ticlid is only to be used in patients who fail aspirin therapy or who are allergic or intolerant to aspirin. Clopidogrel is labeled as a first-line option, along with aspirin, for the prevention of stroke. Ticlid's role in stroke prevention is therefore questionable, if its sole purpose is as an alternative to aspirin for only those patients who are intolerant to or have failed aspirin therapy. If Ticlid offers no advantage over aspirin, it is difficult to defend keeping it on the market with its increased safety risk and all of the precautions associated with its safe use.

Roche believes the results of their benefit-risk analysis will assist them in addressing the issue of first- versus second-line therapy. In the analysis, they estimate the number of strokes prevented by Ticlid minus the excess adverse event mortality (deaths) associated with Ticlid. If the risk-benefit analysis demonstrates that more lives are saved with Ticlid, Roche might use this to support an argument for first-line therapy. Roche, however, does not want nor do they intend to promote Ticlid as superior to other options for the prevention of stroke. Instead, they believe Ticlid should be designated as one of several agents available for stroke prevention for which certain patient populations might have an increased benefit. They believe the physician should decide which stroke-prevention agent is most appropriate for a particular patient and that Ticlid should be one of several options. Dr. Fenichel noted that this is not the definition of second-line therapy and is, therefore, not what the current labeling for Ticlid indicates.

- The current Ticlid labeling makes the recommendation to avoid Ticlid if aspirin can be used. It currently, therefore, is not up to the physician to decide which stroke agent to prescribe. For this decision to be the physician's, Ticlid has to be first-line therapy.

Dr. Fenichel noted that first-line is not the same as first-choice and that a product can be first line without being first-choice. Dr. Fenichel noted that there are many marketed anti-hypertensives and that the labeling does not say which ones are preferable and in which patient populations. Dr. Fenichel further compared this situation to that of medical management versus surgical intervention in certain cardiac conditions. Neither option is first- or second-line. Each option has its benefits and risks and the physician must assess both to determine which treatment is best for a particular patient.

Roche noted that they had probably confused first-line with first-choice and that while they do not necessarily believe Ticlid should be designated as first choice in stroke prevention, they do believe it should be a first-line option.

Discussion Point #5: Comparison of clopidogrel and ticlopidine

Clopidogrel and ticlopidine appear to be very similar compounds with very similar metabolites. A comparison of clopidogrel and ticlopidine in stroke, however, will be difficult, as there are no head-to-head comparison data available. Because Sanofi owns the CAPRIE data, the data are unavailable to Roche. Roche does have, however, a copy of the Agency's medical/statistical review of the CAPRIE data from the clopidogrel NDA and the Advisory Committee Meeting materials from the Clopidogrel Advisory Committee Meeting.

Discussion Point #6: Stent supplement

An efficacy supplement, rather than a labeling supplement, would probably be needed for an indication in stenting, although this should be further discussed with Dr. Temple. The Division was not prepared to say what would be necessary for a stent supplement, and recommended that Roche also ask Dr. Temple about this at the meeting. It might be helpful for Roche to provide at the meeting a list of the published studies they might

Minutes of a teleconference

Date: March 10, 1999

Product: Ticlid (ticlopidine) Tablet (NDA 19-979)

Sponsor: Hoffmann-LaRoche, Inc.

Purpose: progress update on steps taken by sponsor and Division in the reevaluation of Ticlid's place in the market

Teleconference Chair: Raymond Lipicky, M.D.

Teleconference Recorder: Colleen LoCicero

Participants:

FDA

Raymond Lipicky, M.D.	Director, Division of Cardio-Renal Drug Products (HFD-110)
Robert Fenichel, M.D., Ph.D.	Deputy Director, HFD-110
Colleen LoCicero	Consumer Safety Officer, HFD-110

Roche

Dr. Kim Thacker	Medical Director
Dr. Attila Kursun	Medical Director
Dr. Diogini Maladorno	Drug Safety
Mr. Al Masucci	Marketing
Ms. Paula Meade	Marketing
Dr. Don Maclean	Regulatory
Ms. Peggy Jack	Regulatory

Background

This teleconference was arranged so that the Division could update Roche on the steps we had taken so far in our reevaluation of Ticlid's place in the market, and in preparation for a possible advisory committee meeting on this topic.

The teleconference

The Agency has been attempting to determine whether an argument can be made, and if so what that argument is, for keeping Ticlid on the market in light of its hematological

adverse effects and the availability of a similar drug with a better safety profile. Dr. Lipicky noted that this situation is similar, but not identical, to that of terfenadine.

Discussion Point #1: First versus second line therapy

The Agency believes it will be difficult to defend keeping Ticlid on the market if it remains second-line therapy, and is therefore trying to determine if a plausible argument can be made for making Ticlid first-line therapy for the prevention of stroke. The Agency might re-label Ticlid as first-line therapy, if the data supports this. Presently, according to product labeling, both clopidogrel and aspirin are designated first-line therapy for stroke prevention, while Ticlid is designated second-line therapy, to be used only in those patients who have failed aspirin or are intolerant of or allergic to aspirin. For stroke prevention, with regards to aspirin and clopidogrel, the Agency recommends clinicians use either clopidogrel or aspirin and makes no recommendation with regards to one versus the other. The decision of which product to use is entirely up to the clinician. FDA, however, does recommend, with regards to aspirin and ticlopidine, that the clinician prescribe aspirin instead of ticlopidine, unless the patient has previously failed aspirin or is intolerant of or allergic to aspirin. In other words, according to product labeling, aspirin and clopidogrel, as first-line agents in stroke prevention, are comparable, while ticlopidine, as second-line therapy, is inferior to both. This situation makes it difficult to defend keeping Ticlid on the market.

Roche does not believe that clopidogrel is as effective as ticlopidine in the prevention of stroke and, therefore, does not believe clopidogrel can be substituted for ticlopidine in this setting. Roche believes there is a risk associated with ticlopidine use. They however, also believe that if it can be demonstrated that Ticlid saves more lives or prevents more strokes than aspirin, it would be acceptable to keep Ticlid on the market as second-line therapy, provided prescribing clinicians are educated regarding its hematological effects.

If, as Roche believes, the data indicates that ticlopidine is significantly better at preventing strokes than aspirin, then the benefits of increased stroke prevention might outweigh the hematological risks, allowing Ticlid to be first-line therapy. The Agency does not believe it would be reasonable for Ticlid to remain second-line therapy, behind clopidogrel, if Ticlid is shown to be superior to aspirin and clopidogrel is not. If it can be shown that Ticlid is superior to clopidogrel in preventing stroke, the Agency does not believe it would be reasonable to deny those patients who have not failed aspirin therapy or are not intolerant of or allergic to aspirin (presumably a majority of the patients at risk) the increased benefit of Ticlid.

If it is shown that Ticlid is superior to aspirin in stroke prevention, ticlopidine should then be compared for efficacy to clopidogrel.

Once they have concluded their benefit/risk analysis and if it supports a reevaluation of Ticlid's second-line status, Roche intends to do this.

Discussion Point #2: Safety of clopidogrel

The Agency is relatively sure of clopidogrel's safety. In CAPRIE, hematological safety events were closely monitored. The incidence rate for neutropenia was found to be approximately 100 times less than that associated with Ticlid. While the post-marketing period for clopidogrel is shorter than that for Ticlid, the post-marketing experience so far has paralleled that of CAPRIE with regards to agranulocytosis and we, therefore, do not expect any surprises with regards to this as the post-marketing period continues.

Discussion Point #3: Bioequivalence issue

Roche believes the approved dose and regimen for clopidogrel (75 mg once daily) is not equipotent to the approved dose and regimen for Ticlid (250 mg twice a day), and that this could account for clopidogrel's smaller treatment effect and fewer hematological adverse events. They believe that, if dosed properly, Ticlid and clopidogrel would have similar treatment effects and hematological adverse event rates, and are studying this.

Discussion Point #4: Stent indication

If it is not possible to make an argument for Ticlid as first-line therapy in stroke prevention, the Agency believes Ticlid will need a new indication to stay on the market. The Agency noted that the least controversial setting for Ticlid is probably in stent placement, and is perplexed as to why Roche has not pursued an indication in this setting. The Agency is entertaining the thought of bringing before the advisory committee the recommendation to require Roche, via a Federal Register Notice, to include information in labeling on the use of Ticlid in stent placement, or be misbranded. Roche asked if it would be helpful for them to submit a supplement for an indication in stent placement. The Agency noted that it would be helpful. Roche asked what the Agency would require to support a stent indication. The Agency was not sure, at this point, what would be required. Dr. Throckmorton is compiling a bibliography of the available stent studies, and Dr. Lipicky recommended that Roche collaborate with him on this.

Discussion Point #5: Plan

The Agency does not have a position yet with regards to the issue of Ticlid's place in the market and we need to explore all available options. The Agency believes that to effectively address this issue, it is important for the Agency and Roche to work together, so that we are looking at the same studies and working in the same direction. Since we will miss the April Advisory Committee meeting, we will probably take this issue to the July Advisory Committee. The advisory committee meeting will be most productive if both the Agency and Roche are prepared for the meeting and have addressed any

Minutes of a Meeting

Date of Meeting: April 29, 1998
Application: NDA 19-979
Ticlid (ticlopidine) tablets

Sponsor: Hoffmann-LaRoche

Purpose: to discuss labeling changes and Dear Doctor letter

Meeting Chair: Robert Temple, M.D.

Meeting Recorder: Colleen LoCicero

Participants

FDA

Robert Temple, M.D.	Director, Office of Drug Evaluation I (HFD-101)
Raymond Lipicky, M.D.	Director, Division of Cardio-Renal Drug Products (HFD-110)
Robert Fenichel, M.D.	Deputy Director, HFD-110
Stephen Fredd, M.D.	Deputy Director, HFD-110
Lilia Talarico, M.D.	Director, Division of Gastro-Intestinal and Coagulation Drug Products (HFD-180)
Harold Davis, M.D.	Medical Officer, Division of Pharmacovigilance and Epidemiology (HFD-733)
Evelyn Rodriguez, M.D.	Branch Chief, HFD-733
Bram Zuckerman, M.D.	Medical Officer, Center for Devices and Radiological Health (HFZ-450)
David Graham, M.D.	Medical Officer, HFD-733
Mary Fanning, M.D.	Medical Officer, Office of Generic Drugs (HFD-600)
Barry Poole	Branch Chief, Office of Training and Communications (HFD-210)
Min Chen	Supervisory Pharmacist, Division of Pharmacovigilance and Epidemiology (HFD-735)
Katherine Bennett, Pharm D.	Postmarketing Safety Evaluator, HFD-735
Mary Mease	Postmarketing Safety Evaluator, HFD-735
Rita Hassall	Senior Program Manager, HFD-600
Janet Norden	Regulatory Review Officer, Division of Drug Marketing, Advertising, and Communications (HFD-40)
Susan Cruzan	Public Affairs Specialist, Office of Public Affairs and Press Office (HFI-20)
Lee Zwanziger	Team Leader, CDER Executive Secretary (HFD-006)
Colleen LoCicero	Consumer Safety Officer, HFD-110

Hoffmann-LaRoche

Margaret Jack	Program Director, Drug Regulatory Affairs
Ko-Chin Khoo	Clinical Investigations and Drug Metabolism

Attila Kursun, M.D.
Al Masucci
Don MacClean, M.D.
Kim Thacker, M.D.
Philip Villavicencio

Medical Director
Product Director
Regulatory
Medical Director
Market Research

Background

Ticlid is an anti-platelet agent currently indicated to reduce the risk of thrombotic stroke (fatal or nonfatal) in patients who have experienced stroke precursors, and in patients who have had a completed thrombotic stroke where aspirin can not be tolerated or is not indicated. Currently, thrombotic thrombocytopenic purpura (TTP) is cited in the "Warnings" section of the package labeling as a possible, but rare, adverse reaction that can sometimes be fatal.

Recently the FDA was made aware that the incidence of ticlopidine associated TTP is greater than the FDA previously thought and requested labeling changes that would reflect this. This meeting has been arranged to discuss these labeling changes, the drafting of a Dear Doctor letter reflecting the agreed to labeling changes, and issues relating to the use of ticlopidine in stenting.

The meeting

The FDA's goal for this meeting was to come to an agreement with Hoffmann-LaRoche on the labeling changes necessary for Ticlid, at least to the extent that a Dear Doctor letter could be drafted.

Discussion Point #1: Diagnosing TTP

...viewed the process for detecting and diagnosing TTP. He explained that TTP is often difficult to detect and diagnose and, therefore, questioned the reported cumulative presence of TTP. He noted that the sponsor's periodic Safety Reports and Dr. Charles Bennett's Annals of Internal Medicine article include 18 cases that do not meet the criteria for diagnosis of TTP. ... also pointed out that the prognosis of TTP has improved in recent years as a result of successful treatment with plasmapheresis and that early recognition and intervention are essential for successful treatment.

... did not believe that more frequent monitoring of platelets (once weekly versus once every 2 weeks, as is recommended in the current labeling) would significantly improve efforts to detect TTP early because the onset of the disease is usually abrupt and the syndrome is very variable in its presentation. Clinical symptoms can precede laboratory findings and vice-versa ... believed the more important point to incorporate in the labeling was the need to include a peripheral smear, along with the platelet count, hemoglobin and hematocrit, as part of laboratory monitoring, so that the lab can look for the presence of schistocytes (fragmented rbc's) in the peripheral smear. Schistocytes are pathognomonic of TTP, and their appearance often precedes other laboratory findings signaling TTP, such as a reduction in platelets. The FDA and Roche agreed that the new labeling should identify a peripheral smear as part of the essential laboratory monitoring, state that the presence of schistocytes in the peripheral smear is a sign of TTP, and emphasize that laboratory signs may precede clinical symptoms or vice-versa in this syndrome.

Discussion Point #2: Reason for requesting revised labeling at this time

Until recently the FDA had believed that the incidence of ticlopidine associated TTP was relatively rare, one in tens to hundreds of thousands. Recent evidence of higher rates associated with stenting raised the question of whether rates in patients being treated for stroke were really higher also. Evaluation of cases in our sites, together with reasonable estimates of ticlopidine exposure and rates of reporting have led us to conclude that the rate is closer to one in several thousand. Current labeling does not reflect a rate of this magnitude and the FDA is now requesting labeling changes to correct the situation. The current labeling does not sufficiently emphasize the occurrence of this potentially deadly, but treatable, adverse reaction. The FDA believes TTP should be included in the Warning Box of the package insert. Also, the Warning Box should be moved to the beginning of the package insert as is now customary. These actions should make it more likely that this potential adverse event will receive the appropriate level of attention from practitioners.

Discussion Point #3: Rate of incidence

Using a 10 % adverse event reporting rate, Roche has estimated the incidence of ticlopidine associated TTP to be approximately 1 in 5000, whereas the FDA has estimated the incidence to be closer to 1 in 2-3000.

Roche and the FDA agreed that the numerators (number of TTP cases occurring in patients exposed to Ticlid) used by both were similar (88 (Roche) versus 110 (FDA)).

For its denominator, Roche used the total number of new Ticlid prescriptions filled to date. Roche believed this was the best estimate of the total number of patients exposed to Ticlid.

The FDA argued that this number, which includes new prescriptions filled by patients already on Ticlid because their refills have run out or their current prescription is too old to be refilled, gives an inflated denominator. Epidemiology studies indicate that the number of new Ticlid prescriptions filled by patients already taking Ticlid is, roughly, year. This would reduce the denominator used by Roche by a factor of . The FDA believes a truer estimate of the actual number of patients exposed to Ticlid to be between . resulting in a 1 in 2-3000 rate of incidence. The FDA believes this to be the more accurate estimate of incidence and is the one that should appear in the labeling.

Discussion Point #4: Other labeling changes

Roche and the FDA agreed that the revised labeling should indicate to both patients and physicians that ticlopidine associated TTP is most likely to occur after 3-4 weeks of Ticlid therapy.

The FDA agreed to Roche's deletion of "where indicated to prevent stroke" at the end of the last sentence of the second paragraph in the Indications section of the April 20 draft labeling proposed by the FDA.

The FDA agreed with Roche's proposal to include in the contraindications those people with a history of TTP.

Discussion Point #5: Use of ticlopidine in stenting

Roche asked the FDA for recommendations on how to pursue an indication for the use of ticlopidine in stenting, a widespread off-label use. The FDA recommended that Roche

obtain a right to reference data obtained by _____ a major stent manufacturer, on the use of ticlopidine in this setting, as well as the data from the 1996 New England Journal of Medicine article by Schomig et al entitled "A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents."

Conclusion

The FDA and Roche agreed that the FDA will rewrite the Ticlid labeling, while Roche drafts a Dear Doctor letter reflecting the labeling changes agreed upon at this meeting. A copy of the labeling marked-up by Dr. Temple during the meeting will be given to Roche after the meeting. A copy of the revised labeling Roche presented at this meeting will be given to the FDA after the meeting, as well.

Roche will send an electronic copy of the revised labeling they presented. The FDA will send Roche new draft revised labeling by the end of the week. Roche will send the FDA a copy of their draft Dear Doctor Letter as soon as it is ready. If there is disagreement between the FDA and Roche on the revised labeling or the Dear Doctor letter, the labeling and/or letter may be revised and exchanged again. If there is further disagreement, another meeting or teleconference may be necessary.

Signature, Minutes Preparer: _____ Colleen LoCicero

Signature, Meeting Chair: _____ Robert Temple, M.D.

cc: orig. NDA
HFD-110
HFD-110/CLoCicero
HFD-110/SBenton

Drafted: 5/19/98 Finalized: 5/29/98

RD:

Lipicky
Fenichel 5/20/98
Fredd 5/19/98
Talarico
Davis
Rodriguez
Zuckerman
Graham
Fanning
Poole
Chen
Bennett
Mease
Hassall
Norden 5/20/98
Cruzan
Zwanziger

Minutes of a meeting

Date: April 22, 1999

Product: Ticlid (ticlopidine) Tablet
NDA 19-979

Sponsor: Syntex, U.S.A., Inc.

Purpose: to exchange information regarding our preparation for a possible
July Advisory Committee Meeting and discuss what would be
needed for a stent submission

Meeting Chair: Robert Temple, M.D.

Meeting Recorder: Colleen LoCicero

Participants:

FDA

Robert Temple, M.D.	Director, Office of Drug Evaluation I (HFD-101)
Robert Fenichel, M.D., Ph.D.	Deputy Director, Division of Cardio-Renal Drug Products (HFD-110)
Stephen Fredd, M.D.	Deputy Director, HFD-110
Charles Ganley, M.D.	Team Leader, Medical, HFD-110
Douglas Throckmorton, M.D.	Medical Officer, HFD-110
Albert DeFelice, Ph.D.	Team Leader, Pharmacology, HFD-110
Jim Hung, Ph.D.	Statistician, Division of Biometrics I (HFD-710)
Allen Brinker, M.D., M.S.	Medical Officer, Division of Drug Risk Evaluation I (HFD-736)
Katherine Bennett, Pharm.D.	Post-marketing Safety Evaluator, HFD-736
Colleen LoCicero	Consumer Safety Officer, HFD-110

Hoffmann LaRoche, Inc.

Dr. Kim Thacker	Medical Director, Roche Laboratories
Dr. Attila Kursun	Medical Director, Roche Laboratories
Dr. Dionigi Maladorno	Director, Drug Safety
Dr. Samuel Erny	Director, Drug Safety
Mr. Al Masucci	Project Leader, Marketing
Mr. Steve Lee	Director, Statistics and Data Management
Ms. Peggy Jack	Program Director, Drug Regulatory Affairs
Ms. Lynn DeVenezia-Tobias	Program Manager, Drug Regulatory Affairs

Background

This meeting was requested by the Agency to exchange information with Roche on our reevaluation of Ticlid's role in today's market and our preparation for a possible July Advisory Committee Meeting. Roche also requested to discuss what would be expected of a submission for a stent indication.

Meeting

Roche presented their current working hypothesis on the use of Ticlid in the prevention of recurrent stroke and a summary of their supporting efficacy and safety information (see attached slide presentation). In addition, they presented their current working hypothesis on the use of Ticlid in stent placement and a summary of their supporting efficacy and safety information (see attached slide presentation).

Discussion Point #1: Ticlopidine Aspirin Stroke Study (TASS) Efficacy

The primary endpoint for TASS was the composite of death from any cause, and nonfatal stroke. Secondary endpoints were 1) fatal or nonfatal stroke, 2) all-cause death, 3) vascular death, and 4) vascular death, nonfatal stroke, or nonfatal myocardial infarction. The TASS data analysis was by a treatment analysis and not a full intention-to-treat analysis.

TASS was a study of ticlopidine versus aspirin for the prevention of stroke. A big treatment effect for ticlopidine was seen at one year, but the effect decreased thereafter. It was clear that ticlopidine would have been superior in efficacy to placebo had one been present in this study, but it was not so clear that ticlopidine was superior to aspirin. At one year ticlopidine was shown to be significantly more effective than aspirin, but the primary timepoint was at three years where the significance was marginal.

Dr. Fredd noted the primary endpoint included cardiovascular deaths, but when cardiovascular deaths plus stroke was analyzed, the result was not significant. The Advisory Committee recommended approval of Ticlid because it was effective for prevention of stroke in patients with premonitory symptoms. The results of CATS supported the results of TASS. Safety, however, was a major concern.

The Agency asked Roche what they knew about the efficacy of ticlopidine versus aspirin in patients who qualified for enrollment because they had experienced a TIA versus those who qualified because they had experienced a completed stroke. Roche did not know, but are currently investigating this.

Subgroup information from the TASS study seemed to indicate an increased benefit and less toxicity with ticlopidine in African-Americans. The information presented, however, also indicates that Ticlid has its greatest effect in high-risk patients. What percent of

African Americans in the TASS study were high-risk is not known. This makes it difficult to determine if the increased benefit is due to racial differences or to the fact that most of the African-Americans in the study were high-risk. There is an ongoing African-American stroke study that should shed further light on the benefits and risks in African-Americans (see below).

Discussion Point #2: TASS safety

The rate of neutropenia in TASS was lower than the 2.4% reported in the Ticlid labeling. Frequent and reliable CBC monitoring in the TASS study might have averted some of the severe cases of neutropenia, contributing to the lower rate. CBC monitoring was performed every two weeks in TASS.

Discussion Point #3: Canadian American Ticlopidine Study (CATS)

The analysis of the CATS data was presented by Roche as a treatment analysis and not a full intention-to-treat analysis. In the intention-to-treat analysis, ticlopidine was marginally more effective than placebo in patients who experienced a previous stroke.

Discussion Point #4: African American Antiplatelet Stroke Prevention Study (AAASPS)

This study is approximately half completed. There are 700 patients to enroll (out of a total 1800) and the follow-up on those patients will last a year.

The preliminary findings from this study support the TASS findings of increased efficacy and fewer hematological side effects in the African-American population. Roche did not know whether African-Americans typically experience fewer hematological side effects than other races from drugs with significant hematological toxicity. This information might be difficult to obtain as adverse event report forms might not include race.

Discussion Point #5: Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE)

It is not fair to analyze stroke separately in CAPRIE, as the study was not designed to do so. There were three ways to qualify for enrollment into CAPRIE (recent ischemic stroke, recent myocardial infarction, or symptomatic peripheral arterial disease). The results of the study were not homogenous across the three subgroups. An especially interesting and difficult-to-explain finding was that of an increased benefit in endpoint prevention for those patients receiving clopidogrel who had qualified for the study because of stroke but had also experienced a myocardial infarction.

Discussion Point #6: CAPRIE safety

Ms. Bennett noted that, upon further investigation of the 3 post marketing reports of TTP for clopidogrel (noted by Roche in their presentation), only one could be classified as TTP.

Roche's FOI request for the clopidogrel adverse event report has been expedited.

Discussion Point #7: Stent placement

The results from the STARS and ISAR studies were discussed, as well as Roche's need for a right of reference for the data from [redacted]. A benefit of Ticlid plus aspirin might be supported by these studies. Neither the Agency nor Roche is aware of any ongoing or proposed head-to-head study comparing clopidogrel and ticlopidine in stent placement. While CLASSICS was a study of clopidogrel and ticlopidine in stent placement, it was not an efficacy study, but a safety study. The primary (safety) endpoint was a composite of major bleeding complications, neutropenia, thrombocytopenia, or early discontinuation of study drug due to non-cardiac causes. The study was not powered to look at efficacy.

It is unclear whether the definition for stent thromboses was the same throughout the various stent studies.

The Agency noted that the procedure of stent placement itself is improving and that by itself, without medical intervention, the risk of stent-associated events is decreasing. The historical database upon which Roche would probably rely for a stent indication includes primarily studies that used the old stents. The Agency must be convinced that the argument for ticlopidine in stent placement is maintained for the newer stents.

The reported event rates for ticlopidine and clopidogrel for the secondary (efficacy) endpoint in the CLASSICS study are 0.9% and 1.2%, respectively (see attached abstract).

For both STARS and ISAR, patients were to receive antiplatelet therapy for four weeks post-stent placement, but it is not clear that this actually occurred. It would be helpful to know the duration of anti-platelet treatment the patients in these studies actually received. It would be important to note any differences in efficacy or safety between those patients who received two weeks of Ticlid therapy versus those who received four weeks. It might be that four weeks of Ticlid therapy is more efficacious than two weeks and/or that there are fewer hematological side effects at two weeks. It might also be that the differences in efficacy and safety at two and four weeks of therapy are insignificant.

Discussion Point #8: What is needed for a stent submission

It might be possible to pursue a stent indication by submitting a 505 (b) 2 based on published literature, but that would not be optimal. The Agency would like to review the raw stent data. Roche has contacted [redacted] and requested that [redacted] share their data with the Agency and Roche. [redacted] however, refused, noting that the Agency already has the data. The Agency does have the [redacted] data (at least the efficacy data), but probably cannot reference it for the review of a Roche submission without the permission of [redacted]. Roche should request that [redacted] provide a "right of reference" to the Agency for the STARS and ISAR data. If [redacted] does not agree to

provide this, we probably cannot reference the STARS data for the review of a Roche submission, although that is not clear.

If [redacted] is concerned about the confidentiality of their data, they can contact the Agency for reassurance on this. The Agency will work with Roche and [redacted] to assure that the data are appropriately protected.

The remainder of the supplement should consist of the published reports or references to the reports of ticlopidine in stent placement. Roche intends to use the dose regimen from the STARS study for the stent indication.

Discussion Point#9: Compliance with monitoring

The Agency asked Roche whether they had any indication of how compliant patients/physicians were with the recommended monitoring. The Agency noted that the adverse events appear to peak at four week intervals, rather than two week intervals as would be expected if patients are being monitored every two weeks.

Roche believed Dr. Bennett's efforts to inform the medical community about the risk of ticlopidine-associated TTP and the importance of monitoring has greatly increased physician awareness of the hematological risks associated with Ticlid and the importance of frequent, routine monitoring for the first 3 months of therapy. Roche assessed physician awareness of the recommended monitoring last year and found it to be high. Roche further noted that they can look at those patients for whom they are providing free CBC monitoring to assess their compliance, although this group might not be representative of the general Ticlid patient population.

Discussion Point #10: Miscellaneous

The Agency has not performed a formal benefit-risk analysis and has not designated anyone to do so. Roche can contact Ms. LoCicero for information they need regarding the Ticlid issues. The Agency will notify Roche if we do plan to conduct a formal analysis and will inform them as to who will be doing the analysis.

Epidemiology is currently looking at the use of both clopidogrel and ticlopidine. They are reviewing who receives these drugs and the duration of treatment.

Conclusion

The Agency encouraged Roche to contact [redacted] for the right to reference their stent data and continue to pursue a stent indication.

It will probably be necessary to meet again, prior to an Advisory Committee Meeting, to further discuss the Agency's and Roche's reevaluation of Ticlid. Roche was encouraged to contact the Agency when they are prepared for a follow-up meeting.

Signature, Meeting Recorder: /S/ Colleen LoCicero

Concurrence, Meeting Chair: /S/ Robert Temple, M.D.

cc: orig NDA 19-979

HFD-110

HFD-110/LoCicero

HFD-110/SBenton

drafted: 5/7/99 finalized: 5/26/99

rd:

Temple 5/24/99

Fredd 5/12/99

Fenichel 5/14/99

Throckmorton

Ganley 5/14/99

DeFelice 5/14/99

Hung 5/13/99

Brinker

Bennett 5/12/99

TICLID and Use in the Prevention of Recurrent Stroke

April 22, 1999

Working Hypothesis

- TICLID has demonstrated superior efficacy to aspirin in the reduction of the risk of stroke in patients who have experienced a stroke or stroke precursors. Its use is associated with rare, well-characterized serious adverse events that are generally manageable.
- The benefits of TICLID outweigh the risks.
- Therefore, TICLID has a role as a first line therapy in the prevention of recurrent stroke.

- TICLID is the only agent proven to provide:
 - Superior protection over ASA in the prevention of stroke in patients who have had a stroke or stroke precursors, including TIA
 - Benefit in subpopulations
 - African Americans
 - High Risk

- TICLID is the only agent proven to provide:
 - Additional benefits over ASA and over anticoagulation in the prevention of stent thrombosis following coronary stent procedures

Analysis of use in Stroke Prevention

Stroke: Efficacy

TICLID

- CATS
 - TASS
 - Analysis of Subpopulations
 - Cochrane Collaboration analysis
- #### Clopidogrel
- CAPRIE

Roche Position on Ticlid and Cardiac Stents

- Ticlopidine significantly improves the outcome of coronary stent procedures and saves lives as demonstrated by randomized controlled trials
- There is lack of definitive evidence with any other agent (specifically clopidogrel) in the same setting
- The benefit/risk ratio (in terms of lives saved) is greatly in favor of ticlopidine compared to any other regimen
- Ticlopidine is the gold standard of antiplatelet therapy in stenting as endorsed by professional societies
- Roche intends to revise the labeling of Ticlid so as to include information on stenting

Efficacy of TICLID

	ISAR	STARS
# patients	517	1653
Patient population	High risk of ST	312 enrolled in parallel register; Low risk of ST
Trial design	Following successful stent placement, randomly assigned Rx for 30 days	Following successful stent placement, randomly assigned Rx for 30 days
Primary Endpoint	Death due to cardiac cause or occurrence of MI, CABG, PTCA	Death, revascularization, nonfatal MI (reflected the occurrence of ST)

Efficacy of TICLID

	ISAR	STARS
Medication regimen	• Plavix + ASA • ASA • Ticlid + ASA	• ASA Alone • warfarin + ASA • Ticlid + ASA
Primary Endpoint reached	6.2% plavix + ASA 1.6% Ticlid	3.6% ASA 2.7% warfarin 0.5% Ticlid
Stent Thrombosis	5.4% plavix + ASA 0.8% Ticlid	2.9% ASA 2.7% warfarin 0.9% Ticlid

Clopidogrel

- Retrospective series (Lenox Hill, Mayo)
- CLASSICS
- Is CAPRIE relevant?
 - Stent patients not entered
 - CAD (MI?) sub-group: No benefit demonstrated
- Anecdotal reports of subacute thrombosis with clopidogrel
- Clopidogrel lacks data in large scale randomized controlled trials to support efficacy

Clopidogrel

CLASSICS

1020 patients receiving ASA as background therapy were randomized to receive for 28 days:

- TICLID 250 mg bid
- Clopidogrel loading dose 300 mg + 75 mg QD or
- Clopidogrel 75 mg QD

CLASSICS

- Primary end point (SAFETY):
 - composite of major bleeding complications, neutropenia, thrombocytopenia or early discontinuation for non-cardiac adverse events
- Secondary end point
 - major cardiovascular events including death, MI or urgent revascularization

Stroke Benefit: TICLID

Unique populations: High Risk

Outcome Rate at 5 Years (%)

<u>Risk Group</u>	<u>TICLID</u>	<u>ASA</u>	<u>p-value</u>
I	20	21	.33
II	34	36	.44
III	33	51	.04

TICLID may have greatest effect among high risk patients (age>65, Htn, DM)

TICLID and Use in the African American Population

Ticlopidine Aspirin Stroke Study Efficacy

- 3034 patients including 495 blacks and 108 non-black, non-white patients
- Cumulative event rates (per 100 patients)
 - 48.1% risk reduction relative to ASA for death or nonfatal stroke (year 1)
 - 60.8% risk reduction for fatal or nonfatal stroke (year 1)

Ticlopidine Aspirin Stroke Study Safety

- Safety in Non-white Population
 - No cases of severe or moderate neutropenia in either treatment group
 - Mild neutropenia in 9 patients on TICLID and 7 with aspirin
 - Incidence of all adverse events approx. 10% lower in both groups than overall TASS population

Ticlopidine Aspirin Stroke Study Conclusions

- Risk reductions seen were not statistically significant vs whites due to small sample size yet trend of greater efficacy
- Risk of adverse reactions, particularly neutropenia, is similar in TICLID- and aspirin-treated non-white patients

African American Antiplatelet Stroke Prevention Study AAASPS

- Primary Hypothesis
 - TICLID is more effective than aspirin in the prevention of recurrent stroke, vascular death and MI in middle-aged and elderly African American non-cardioembolic ischemic stroke patients followed for two years
 - Design
 - Multicenter, randomized, double blind trial of 1800 patients randomized to ASA 650 mg/d or TICLID 250 mg BID

Preliminary Aggregate Safety Data for AAASPS

- Presented at AHA International Conference on Stroke and Cerebral Circulation, 1999
- 744 patients enrolled at time of analysis (1092 patients enrolled at present with avg. follow up one year)
- 0.9% rate of neutropenia; none severe and all reversed
- 0 cases of thrombocytopenia or TTP

Clopidogrel

- CAPRIE
 - over 19,000 patients at risk for ischemic events (heterogeneous population)
 - Atrial fibrillation excluded
 - Average follow-up 1.9 years
 - Relative risk reduction 8.7% (p=0.043)
 - Absolute risk reduction 0.51% per year
 - Heterogeneity across subgroups (p=0.042)

Clopidogrel: CAPRIE

Distribution of Vascular Events (fatal and nonfatal)

Subgroup	Stroke	MI	Other Vasc Death
Stroke			
clop.	73%	10%	17%
ASA	73%	11%	16%

Clopidogrel: CAPRIE

Distribution of Vascular Events (fatal and nonfatal)

Subgroup	Stroke	MI	Other Vasc Death
MI			
clop.	14%	56%	30%
ASA	15%	61%	24%
PAD			
clop.	38%	32%	31%
ASA	30%	39%	31%

Clopidogrel: CAPRIE

- Stroke subgroup data (6431 patients)
 - Event rate per year:
 - clopidogrel 7.15% (nyears=6054)
 - aspirin 7.71% (nyears=5979)
 - Relative risk reduction 7.3%
 - p = 0.26
- Unable to demonstrate any statistically significant benefit

Safety Analysis

- Adverse Event Distribution Analysis
 - TICLID
 - Clopidogrel
- Information sources:
 - Roche Drug Safety Reports
 - FOI reports
- Review of medically relevant AEs

Safety Profile: Clopidogrel

- Neutropenia
 - 4 patients (of 9599) in CAPRIE with severe neutropenia vs. 2 patients on ASA
 - 2 of these with neutrophil counts of zero vs. 0 on ASA
- TTP
 - Not seen in CAPRIE, however...
 - 5 post marketing reports of at least 3 cases (2 cases of ITP)
- Aplastic Anemia
 - One case seen during CAPRIE (1/9599)

Safety Profile: Clopidogrel

FOI Report (Nov. 97-March 99)

	# of cases
• Pancreatitis	8
• Hepatic Failure	5
• TTP	3 (5 reports)
• ITP	2
• Agranulocytosis	7
• Thrombocytopenia	20
• Guillain-Barre Syndrome	2

Benefit-Risk Analysis

- Comparative evaluation pending:
 - TICLID
 - Clopidogrel

Combination treatment with an ADP receptor antagonist, ticlopidine (T) plus aspirin is currently regarded as the reference antithrombotic therapy for coronary stent implantation. Clopidogrel (C) is a new ADP receptor antagonist that is more potent than T and is free from the haematological adverse events that limit T therapy. The CLASSICS (Clopidogrel Aspirin Stent International Cooperative Study) trial is the first double-blind, randomized study of C in stenting and the first to evaluate the clinical use of C in combination with aspirin.

Methods : 1,020 patients receiving coronary stents were randomized to 28 days of treatment with one of the three regimens ; 1) C 300 mg (loading dose) on day 1, followed by C 75mg o.d. ; 2) C 75 mg o.d. from day 1 ; 3) T 250 mg b.i.d. in addition, all 3 groups received aspirin 325 mg o.d. Antiplatelet therapy was started within 6 hours of stent placement. The primary (safety) endpoint was a composite of major bleeding complications, neutropenia, thrombocytopenia or early discontinuation of study drug due to non-cardiac causes ; the secondary (efficacy) endpoint consisted of major cardiac adverse events (MACE).

Results : Data for the primary and secondary endpoints are as follows :

Endpoint (28 days of treatment)_No of patients (%) with events ___T

(n=340)_C75mg

(n=335)_C300mg

(n=345)_C pooled

(n=680)___Primary (safety)_31 (8.12%)_21 (6.3%)_10 (2.9%)_31 (4.56%)*___Secondary (MACE)_3 (0.9%)_5 (1.5%)§_4 (1.2%)§_ ___* p=0.005, C pooled vs T ; § p=NS between C 75 mg, C 300 mg and T for any of the secondary endpoints (p>0.55)

For the primary endpoint, the difference in event rates between T and C was chiefly due to differences in the frequency of discontinuations due to non-cardiac adverse events, indicating that with C compared with T, more patients will be able to benefit from an optimal regimen for a longer period of time.

In conclusion, the safety/tolerability profile of C is superior to that of T in patients undergoing coronary stenting, with no increase in haemorrhagic complications in patients receiving a C 300 mg loading dose. In CLASSICS, C and T showed comparable efficacy with regards to MACE.

**APPEARS THIS WAY
ON ORIGINAL**