

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

**APPLICATION NUMBER
19-979/S-018**

Correspondence



March 27, 2000

Food and Drug Administration
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
ATTN: DOCUMENT CONTROL ROOM, HFD-110
1451 Rockville Pike, Room 5002
Rockville, Maryland 20852



Ladies and Gentlemen:

Re: NDA 19-979/S-018 - Ticlid® (ticlopidine hydrochloride) Tablets
Response to FDA Request for Information

Reference is made to an inquiry made by Ms. Linda Carter (Office of Drug Evaluation I) concerning the ability of _____ to provide the following information in connection with the STARS clinical trial data that are referenced in the subject supplement:

1. Disclosure of financial interests and arrangements of clinical investigators
2. Debarment certification

Accordingly, we have contacted _____ on several recent occasions and have documented our discussions with them in the three facsimiles that were sent to Ms. Carter on February 11, February 18, and March 2, 2000 (copies attached). We do not expect to receive any further information from _____ in response to Ms. Carter's inquiry.

Please contact the undersigned if you have comments or questions concerning the information we have provided in this submission.

Sincerely,

HOFFMANN-LA ROCHE INC.

Lynn DeVenezia-Tobias

Lynn DeVenezia-Tobias
Program Manager
Drug Regulatory Affairs
(973) 562-5539 Telephone
(973) 562-3700/3554 Fax

*Linda Carter reviewed this
and the sponsor has fulfilled
their obligations with respect to
financial disclosure & debarment
certification. All 3/29/00*

LDT:eh
Attachments
HLR No. 2000-784

Desk Copy: Ms. Colleen LoCicero, Regulatory Health Project Coordinator, HFD-110

Fax Cover Sheet



Pharmaceuticals

To: Ms. Linda Carter Tel. (301) 594-6758
Food and Drug Administration Fax (301) 594-5298
Office of Drug Evaluation I

Copies:

From: Lynn DeVenezia-Tobias Tel. (973) 562-5539
Program Manager Fax (973) 562-3700/3554
Drug Regulatory Affairs

Date: February 11, 2000

No. of pages: 1 (incl. cover sheet)

Re: NDA 19-979/S-018 - Ticlid® (ticlopidine hydrochloride) Tablets
Supplemental New Drug Application for New Indication

Dear Ms. Carter:

Reference is made to your inquiry regarding the availability of the following information from _____ in connection with the STARS clinical trial data that are referenced in the subject supplement:

1. Disclosure of financial interests and arrangements of clinical investigators
2. Debarment certification

_____ has informed me that the STARS trial was initiated and completed prior to the final rule for financial disclosure of clinical investigators. Thus, the information was not collected and would be difficult, if not impossible, to construct at this time.

_____ has also informed me that, to the best of their knowledge, they did not use in any capacity the services of any person debarred in connection with the STARS trial. It was explained that under _____ policy this would have been a prohibited act. _____ also mentioned that preparation of a debarment certification was not a requirement for a device application.

Please contact me at the listed numbers if you have any comments or questions concerning this information.

Regards,

Lynn

HLR No. 2000-371

Fax Cover Sheet



Pharmaceuticals

To: Ms. Linda Carter Tel. (301) 594-6758
Food and Drug Administration Fax (301) 594-5298
Office of Drug Evaluation I

Copies:

From: Lynn DeVenezia-Tobias Tel. (973) 562-5539
Program Manager Fax (973) 562-3700/3554
Drug Regulatory Affairs

Date: February 18, 2000

No. of pages: 2 (incl. cover sheet)

Re: NDA 19-979/S-018 - Ticlid® (ticlopidine hydrochloride) Tablets
Supplemental New Drug Application for New Indication

Dear Ms. Carter:

Reference is made to my fax dated February 11, 2000 and to our telephone conversation on February 16, 2000 regarding your inquiry about the availability of the following information from _____ in connection with the STARS clinical trial data that are referenced in the subject supplement:

1. Disclosure of financial interests and arrangements of clinical investigators
2. Debarment certification

In response to your inquiry about the number of investigators participating in the STARS clinical trial and the number of subjects treated at each study site, informed me in a correspondence that I received today that all of the STARS clinical trial data have been previously provided to FDA (i.e., Center for Devices and Radiological Health under PMA P900043/S8 (and subsequent amendments thereto) and Dr. Stephen Fredd, Division of Cardio-Renal Drug Products). Thus, FDA is in possession of all the STARS data that are available. _____ mentioned that it would be difficult to provide additional information regarding the financial disclosure of clinical investigators as they do not have resources that can be devoted to addressing the issue.

In response to your request for an appropriate debarment certification, _____ has also informed me that they do not have resources that can be devoted to obtaining information about debarred individuals, and suggested that I research this on my own. Accordingly, I performed an internet search and located the FDA/ORR Debarment List from the FDA Home Page. I then compared this list to the names of the principal

investigators and study coordinators who participated in the STARS study, the publication of which Roche provided in the supplemental new drug application:

Leon MB, Baim DS, Popma JJ, et al. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. N Engl J Med 1998; 339:1665-71.

I did not find any names in this literature reference to be on the debarment list. Note regarding study details: the study was conducted between February 1996 and November 1996 and involved 50 centers.

Please contact me at the listed numbers if you have any comments or questions concerning this information.

Regards,

Lynn

HLR No. 2000-442

Fax Cover Sheet



Pharmaceuticals

To: Ms. Linda Carter Tel. (301) 594-6758
Food and Drug Administration Fax (301) 594-5298
Office of Drug Evaluation I

Copies:

From: Lynn DeVenezia-Tobias Tel. (973) 562-5539
Program Manager Fax (973) 562-3700/3554
Drug Regulatory Affairs

Date: March 2, 2000

No. of pages: 2 (incl. cover sheet)

Re: NDA 19-979/S-018 - Ticlid® (ticlopidine hydrochloride) Tablets
Supplemental New Drug Application for New Indication

Dear Ms. Carter:

Reference is made to my fax dated February 18, 2000 and to our telephone conversation on February 28, 2000 regarding your inquiry about the availability of the following information from [redacted] in connection with the STARS clinical trial data that are referenced in the subject supplement:

1. Disclosure of financial interests and arrangements of clinical investigators
2. Debarment certification

In response to your inquiry about the disclosure of financial interests and arrangements of clinical investigators, [redacted] informed me in a recent correspondence that their ability to provide such a certification is not possible. [redacted] maintained that they would have no right or authority to know or request whether the investigators had any proprietary interests in Ticlid, which was not their product, during the conduct of the STARS trial.

According to [redacted] it is important to note that the STARS trial was a 3-arm, randomized study involving over 1600 patients. Although randomization does not eliminate all sources of potential bias, [redacted] believes that it certainly reduces the opportunity for bias rather significantly.

At your suggestion, I also spoke with a Roche patent attorney about this issue. Following our conversation, I can confirm that Syntex (U.S.A.) Inc. (the patent owner) has not licensed anyone in the United States under the patent besides Hoffmann-La Roche Inc.

Please contact me at the listed numbers if you have any comments or questions concerning this information.

Regards,

Lynn

HLR No. 2000-561

Memo to the file

Date:

SEP 20 2000

9/19/00

From:

Colleen LoCicero
Regulatory Health Project Manager, HFD-110

/S/

Through:

James Hung, Ph.D.
Team Leader, Statistical, HFD-710

/S/ 9/19/00

Douglas Throckmorton, M.D.
Deputy Director, HFD-110

/S/ 9/15/00

Raymond Lipicky, M.D.
Director, HFD-110

/S/ 9/20/00

To:

NDA 19-979/SE1-018

Subject:

Need for DSI audit of STARS study

In his center-by-center analysis of the STARS data (analysis of the number of participants and events per site), Dr. Hung concluded that the results were not dependent on any one site. Elimination of any one site would not appreciably change the study results. Therefore, a DSI audit of this study is not warranted and will not be requested.

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

Memo to the file

Date: February 27, 2001
From: Colleen LoCicero, RHPM
To: NDA 19-979/SE1-018
Subject: Dr. Hung's revised STARS table

On January 3, 2001, I telephoned the sponsor to request that they recalculate and revise the odds ratios and p-values for the first STARS table in the proposed labeling for this supplemental application, based on the changes to the table they proposed in their January 5, 2001 draft labeling submission.

On February 16, 2001, the sponsor faxed to the Division a revised STARS table. Drs. Throckmorton and Hung reviewed the table. Dr. Hung recommended a few changes be made to the table and on February-21, 2001, I faxed to the sponsor the STARS table, as revised by Dr. Hung.

Subsequently, I received a telephone call from Ms. Lynn DeVenezia-Tobias of Hoffmann-La Roche regarding Dr. Hung's changes. I recommended that Ms. DeVenezia-Tobias speak with Dr. Hung directly to discuss the changes, which she indicated she would likely do. I informed Dr. Hung of Ms. DeVenezia-Tobias' plans. Prior to a discussion with the Ms. DeVenezia-Tobias, however, Dr. Hung reconsidered the changes to the table he recommended, concluding that the sponsor's table was acceptable as it was and did not need to be revised.

I related Dr. Hung's decision to the sponsor in a voicemail for Ms. DeVenezia-Tobias on February 21, 2001. I indicated that my next step with respect to this supplemental application would be to send the revised labeling and table up to Dr. Temple for his review and comment.

**APPEARS THIS WAY
ON ORIGINAL**

**DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION**



US Mail address:
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

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Transmitted to FAX Number: (973) 562-3700
Attention: Lynn DeVenezia-Tobias
Company Name: Hoffmann-La Roche Inc.
Phone: (973) 562-5539
Subject: revised Ticlid table
Date: 2/21/01
Pages including this sheet: 2
From: Colleen LoCicero
Phone: 301-594-5332
Fax: 301-594-5494

Lynn,

As I mentioned in the voicemail I left you earlier this morning, Dr. Hung has made some changes to the STARS table (first table in the **CLINICAL TRIALS/Stent Patients** subsection of the Ticlid labeling) proposed in your February 16, 2001 faxed correspondence. The revised table accompanies this cover sheet.

Regards,
Colleen

STARS	TICLID + Aspirin N=546	Aspirin N=557	Coumadin + Aspirin N=550	Odds Ratio (95% C.I.)*	p-Value*
Primary Endpoint	3 (0.5%)	20 (3.6%) 21 (3.8%)	15 (2.7%)	0.15 (0.03, 0.51) 0.14 (0.04, 0.48)	<0.001
Deaths	0 (0%)	1 (0.2%)	0 (0%)	---	---
Q-Wave MI (Recurrent and Procedure Related)	1 (0.2%)	12 (2.2%)	8 (1.5%)	0.08 (0.002, 0.57)	0.004
Angiographically Evident Thrombosis	3 (0.5%)	16 (2.9%)	15 (2.7%)	0.19 (0.03, 0.66)	0.005

*Comparison of TICLID plus aspirin to aspirin alone.

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Fax Cover Sheet



Pharmaceuticals

To:	Ms. Colleen LoCicero Regulatory Health Project Manager Division of Cardio-Renal Drug Products	Tel. (301) 594-5332 Fax (301) 594-5494
Copies:	-	
From:	Lynn DeVenezia-Tobias Program Manager Drug Regulatory Affairs	Tel. (973) 562-5539 Fax (973) 562-3700/3554
Date:	February 16, 2001	
No. of pages:	2 (incl. cover sheet)	

Re: **NDA 19-979/S-018 - Ticlid® (ticlopidine hydrochloride) Tablets**
Response to Request for Data

Dear Colleen:

Reference is made to the submission we made on January 5, 2001 (Amendment to Supplement S-018 - Revised Draft Labeling) and to a follow-up request the Agency made for Roche to calculate the "Odds Ratio" and "p-Value" in the first STARS table in the revised draft labeling.

In follow-up to the Agency's request, we have now revised the first STARS table in the proposed labeling with data provided by a Roche statistician. Please note that we have also added the terms 'Draft Labeling' to follow the description of ' in the same table to more accurately describe the event.

Please contact me at the listed numbers if you have comments or questions concerning the information we have provided in this facsimile.

Regards,

Lynn

HLR No. 2001- 448

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

**DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION**



US Mail address:
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Transmitted to FAX Number: (973) 562-3700

Attention: Lynn DeVenezia-Tobias

Company Name: Hoffmann-La Roche

Phone: (973) 562-5539

Subject: information requests/NDA 19-979/S-018

Date: 9/20/00

Pages including this sheet: 2

From: Colleen LoCicero
Phone: 301-594-5334
Fax: 301-594-5494

Lynn,

Dr. Throckmorton has an additional request for information, so I am faxing his second request along with his first request (which I left in a voicemail for you this morning). We can wait until next week (week of 9/25) when you are back in the office for your response to these requests. If you have any questions, please let me know.

Thanks,
Colleen

LS

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

Request #1 (this request was also left in your voicemail on 9/20/00 a.m.)

In the 33 trials submitted in the supplement, Dr. Throckmorton identified two trials that looked at the effect of adding Coumadin (or similar anticoagulants) onto a background of other therapies.

STARS compared aspirin alone to aspirin plus Coumadin.

Park et al compared aspirin plus ticlopidine to aspirin plus ticlopidine plus Coumadin.

Please provide any information you have on other trials that made this comparison.

Request #2

In volume 67.1, section 7.2.3, there are data on the incidence of major cardiac events for patients treated with ticlopidine in the prospective cohort studies. Please provide any similar data you have on the pooled comparator groups (aspirin alone or aspirin plus anticoagulant).

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

AUG - 8 2000

**DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION**



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Transmitted to FAX Number: (973) 562-3700
Attention: Lynn DeVenezia-Tobias
Company Name: Hoffmann-LaRoche
Phone: (973) 562-5539
Subject: request for information
Date: 8/8/00
Pages including this sheet: 2
From: Colleen LoCicero
Phone: 301-594-5334
Fax: 301-594-5494

Lynn,

We received the August 4, 2000 fax of your response to Dr. Throckmorton's August 2, 2000 request for information regarding NDA 19-979/S-018. Thank you for your prompt response.

Dr. Hung has reviewed the submitted information. He notes that the tables in your August 4, 2000 fax contain the incidences of death, MI, and reintervention, respectively. What Dr. Hung needs, however, is the incidence of death or MI as a composite endpoint. That is, if a patient had a MI and died later, he/she would be counted as only one event. The separate incidences of death and MI may result in a double count for the composite endpoint if generated from the submitted tables. Please attempt to obtain data on the composite endpoint of death or MI and provide these data to the Agency.

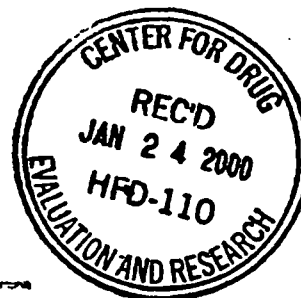
Please let me know if you have any questions.

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January 20, 2000

Food and Drug Administration
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
ATTN: DOCUMENT CONTROL ROOM, HFD-110
1451 Rockville Pike, Room 5002
Rockville, Maryland 20852



Ladies and Gentlemen:

NDA NO. 19-979 REF. NO. 018
NDA SUPPL FOR SEI

**Re: NDA 19-979 - Ticlid[®] (ticlopidine hydrochloride) Tablets
Supplemental New Drug Application for New Indication and
Request for Priority Review**

Ticlid[®] (ticlopidine hydrochloride) Tablets is currently approved under NDA 19-979 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.

Hoffmann-La Roche Inc. has had numerous discussions with the Agency on several occasions last year concerning the submission of information to support a new stent indication. In follow-up to these discussions, we are submitting this supplemental new drug application to provide safety and efficacy data derived from a comprehensive review of the medical literature (see discussion below), together with dosage and administration guidelines, to support the use of Ticlid as adjunctive therapy with aspirin for the prevention of subacute stent thrombosis in patients undergoing successful coronary stent implantation. This is in accord with the Agency's current policy of requesting that sponsors submit supplements with safety and efficacy data on the off-label uses of approved marketed products for the purpose of getting these uses in the product's approved label.

Each year about 655,000 coronary angioplasties are performed in the United States. At least half of these involve the placement of a coronary stent. The administration of the combination of ticlopidine plus aspirin after stent deployment is currently considered the standard of care in this medical setting. Several studies have shown that this combination is superior to alternative antithrombotic medications in preventing subacute stent thrombosis in patients undergoing stent implantation, including high risk patients. The currently approved product labeling, however, does not recommend the concomitant use of Ticlid and aspirin. Coronary stent implantation constitutes a major off-label use of ticlopidine. This supplemental new drug application provides dosage and administration guidelines for the safe and effective use of Ticlid as adjunctive therapy with aspirin for this new stent indication. Based on the extent of the off-label use of Ticlid and aspirin for coronary stents, the lack of safety information in the current Ticlid label regarding the use of this combination therapy, and our belief that Ticlid has the potential for

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providing a significant preventative therapeutic advance as compared to other alternative antithrombotic medications in this medical setting, we are hereby requesting a priority review of the supplement.

A search and review of the published literature identified 44 published articles, the data from which were categorized into one or more of the following clinical study types: controlled, randomized (5), nonrandomized, comparative (5), observational/retrospective (23), pharmacodynamic (7) and case studies for safety only (4). The literature collected for this submission was identified through searches conducted through August 1999. In the published studies providing data on the efficacy of the combination of ticlopidine plus aspirin in coronary stenting, a total of 17,810 patients were involved in 33 individual reports. For safety, a total of 12,977 patients were exposed to ticlopidine plus aspirin and reported in 31 individual reports. We are including in this submission authorization from _____ for the Agency to access clinical data from STARS (Stent Anticoagulation Restenosis Study) on behalf of Hoffmann-La Roche Inc. Concerning ISAR (Intracoronary Stenting and Antithrombotic Regimen Trial), we understand from a previous conversation with Dr. Raymond J. Lipicky, Director, Division of Cardio-Renal Drug Products, that the Agency will independently attempt to obtain permission to access these data in support of this supplemental new drug application, as Roche has been unsuccessful in doing so.

In addressing the December 2, 1998 Pediatric Rule (63 FR 66632), we hereby request a waiver for pediatric study requirements as neither the currently approved indication nor the proposed new indication are applicable to the pediatric population.

This supplement is organized as follows and contains only those sections that are applicable for this submission:

<u>Overall Content</u>	<u>Volume(s)</u>
Section 1 – Application Forms and Index	1
Section 2 – Labeling	1
Section 8/10 – Clinical and Statistical	1-4
Background and Overview of Clinical Investigations	1
Benefits and Risks	1
Integrated Summary of Efficacy Data	1
Integrated Summary of Safety Information	1
Clinical Pharmacology Summary	1
Clinical References Supporting this Supplement	2-4

We do not plan to submit a safety update report as per 21 CFR 314.50 (d) (5) (vi) (b), since data derived from a comprehensive review of the medical literature, not data derived from ongoing clinical studies, were used to support the proposed new indication.



Division of Cardio-Renal Drug Products
January 20, 2000
Page 3 of 3

Supplemental New Drug Application Referencing System:

As many of the documents provided in this supplement refer to the same published literature sources, we have provided a master list of references containing unique reference numbers. Therefore, regardless of where in the supplement a literature citation is referred to it will only have one unique number. Please refer to the Index, Volume 1, of this supplement to determine the location of a particular reference.

Please contact the undersigned if you have comments or questions concerning the information we have provided in this submission.

Sincerely,

HOFFMANN-LA ROCHE INC.

Lynn DeVenezia-Tobias
Program Manager
Drug Regulatory Affairs
(973) 562-5539 telephone
(973) 562-3700/3554 fax

LDT:emd
Attachments
HLR No. 2000-120
User Fee paid December 3, 1999



L. Colleen

Food and Drug Administration
Rockville MD 20857

NDA 19-979/S-018

FEB - 4 2000

Syntex (U.S.A.) Inc.
c/o Hoffmann-La Roche Inc.
Attention: Lynn DeVenezia-Tobias
340 Kingsland Street
Nutley, New Jersey 07110-1199

Dear Ms. DeVenezia-Tobias:

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

Name of Drug Product: Ticlid (ticlopidine hydrochloride) Tablets

NDA Number: 19-979

Supplement Number: S-018

Therapeutic Classification: Standard (S)

Date of Supplement: January 20, 2000

Date of Receipt: January 24, 2000

This supplement proposes the following change: The addition of a new indication to prevent subacute stent thrombosis

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on March 24, 2000 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be November 24, 2000 and the secondary user fee goal date will be January 24, 2001.

As of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). We note your request to waive this requirement on the grounds that neither the currently approved indication nor the proposed new indication are applicable to the pediatric population; we grant this request.

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

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products,
HFD-110
Attention: Division Document Room,
HFD-110
5600 Fishers Lane
Rockville, Maryland 20857


Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products,
HFD-110
Attention: Division Document Room,
HFD-110
1451 Rockville Pike
Rockville, Maryland 20852-1420

If you have any questions, please contact:

Ms. Colleen LoCicero
Regulatory Project Coordinator
(301) 594-5334.

Sincerely yours,


Natalia A. Morgenstern
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research