CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75161

CORRESPONDENCE

ANDA 75-161

Lipha Pharmaceuticals Inc.
U.S. Agent for: Genpharm Inc.
Attention: Anita M. Goodman, M.D.
9 West 57 th Street
Suite 3825
New York, NY 10019-2701

SEP 21 1998

Dear Madam:

This is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Ticlopidine Hydrochloride Tablets, 250 mg.

The reference listed drug (Ticlid®; Hoffman La Roche Inc.) provides educational programs for physicians and patients. In addition, a CBC monitoring program is offered free of charge. The reason for this monitoring is that ticlopidine can cause life-threatening hematological adverse reactions, including neutropenia/agranulocytosis and thrombotic thrombocytopenic purpura (TTP). To detect early signs of these conditions and allow intervention when necessary, it is important that patients receiving ticlopidine be hematologically and clinically monitored every 2 weeks for evidence of neutropenia or TTP during the first 3 months of treatment. The Agency also believes that educational programs that alert physicians to the occurrence of neutropenia/agranulocytosis and TTP can enhance the safe use of ticlopidine and strongly encourages you to consider a similar educational program.

In addition, you were recently notified by the Division of Labeling and Program Support of new and important changes in the package insert labeling for ticlopidine. In addition to these requested labeling changes, we ask that you outline any plans you have in addressing these important issues discussed above.

We await your prompt response. If you have further questions concerning this issue, please contact Mr. Charlie Hoppes, Team Leader - Division II; Labeling Review Branch at (301)827-5846.

Sincerely yours,

/S/ 9/21/98

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 75-161

Par Pharmaceuticals Inc.
Attention: Robert A. Femia, Ph.D.
U.S. Agent for: Genpharm Inc.
One Ram Ridge Road
Spring Valley, NY 10977

Dear Sir:

This is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Ticlopidine Hydrochloride Tablets, 250 mg (Ticlopidine).

In light of several new applicants seeking to market Ticlopidine, inquiries from those applicants, and the November 27, 1998, citizen petition from Hoffmann-LaRoche, Inc., as well as other correspondence, the Agency has reevaluated the measures that it believes may enhance the safe use of Ticlopidine.

Our letter of September 21, 1998, informed you that Hoffman-LaRoche, Inc., manufacturer of the reference listed drug, TICLID® tablets, has in place a number of steps intended to encourage the safe use of their product. These steps include offering free blood monitoring to patients and providing educational materials to health-care professionals to make them aware of potentially life-threatening hematological adverse reactions associated with the drug and to help ensure appropriate monitoring of patients on Ticlopidine.

The Agency has reevaluated the utility of Hoffman-LaRoche's post-marketing program in light of information gathered from their seven years of experience marketing TICLID®. We have concluded that the provision of white cell count monitoring, offered free of charge, does not significantly enhance the safe use of the product. Accordingly, although monitoring remains an important part of the safe use of Ticlopidine, we will not expect applicants to offer this free service in the future. We continue to believe strongly, however, that a post-approval educational program directed towards prescribing physicians and other health-care professionals may enhance the safe use of Ticlopidine.

The Agency believes that an effective educational program for Ticlopidine should include the following characteristics:

1. Target audience for an adequate educational campaign.

    a. Physicians, including those within a health-care system such as an HMO or PPO, who prescribe Ticlopidine.

    b. Other health-care professionals, such as nurse practitioners, physician assistants, and dispensing pharmacists, who are in a position in a given health-care system to educate patients and/or monitor compliance.

2. Substantive elements of an adequate educational campaign.

    a. A clear statement that Ticlopidine is approved for use only in patients who are intolerant or allergic to aspirin therapy or who have failed aspirin therapy.

    b. Discussion of the known risks of Ticlopidine therapy and how to mitigate them. An adequate discussion would include not only information about the frequency and potential severity of adverse events, but also informaiton about the role that clinical observation and blood monitoring can play in preventing/minimizing their clinical severity. The discussion should include information about the following known adverse events:

        (i) Neutropenia/agranulocytosis;

        (ii) Thrombotic thrombocytopenic purpura (TTP); and

        (iii) Aplastic anemia.

    c. Information delineating the schedule for blood and clinical monitoring during the first three months of treatment, and describing the steps to be taken should the results of such monitoring be abnormal.

    d. A statement reinforcing the need for all health-care professionals to report observed serious and fatal adverse events with Ticlopidine administration to MedWatch.

Within 10 days of receiving this notice, we ask that you submit your post-approval plan to address the important issues outlined above. You should be prepared to implement your educational program upon distribution and marketing of Ticlopidine under an approved application. You should also provide, in each annual report, a brief summary of your implementation efforts, as well as any other relevant data, associated with the educational program described above.

We await your prompt response. If you have further questions or need clarification on any of the elements listed above, please contact Mr. Charlie Hoppes, Team Leader - Division II; Labeling Review Branch at (301) 827-5846.

Sincerely yours,

/S/ 6/15/99

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 75-161

JAN 28 2000

Par Pharmaceuticals Inc.
Attention: Robert A. Femia, Ph.D.
U.S. Agent for: Genpharm Inc.
One Ram Ridge Road
Spring Valley, NY 10977

Dear Sir:

This is in reference to your abbreviated new drug application dated July 8, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Ticlopidine Hydrochloride Tablets, 250 mg.

Reference is also made to your amendments dated March 2, April 30, May 6, September 22, October 1, November 11, 1998; and January 7, 1999.

We have completed the review of this abbreviated application and have concluded that, based upon the information you have presented to date, the drug is safe and effective for use as recommended in the submitted labeling. Therefore, the application is **tentatively approved**. This determination is based upon information available to the Agency at this time (i.e., information in your application and the status of current good manufacturing practices (CGMP) of the facilities used in the manufacturing and testing of the drug product), and is therefore, subject to change on the basis of new information that may come to our attention.

The listed drug product referenced in your application is subject to a period of patent protection which expires on May 27, 2003, (Patent No. 4,591,592). Section 505(j)(5)(B)(iii) of the Act provides that approval of an abbreviated application shall be made effective immediately unless an action is brought before the expiration of forty-five days from the date the notice provided under paragraph (2)(B)(I) is received. You have notified FDA that Genpharm Inc. has complied with the requirements of Section 505(j)(2)(B) of the Act by providing the required notice to each patent holder, and that no action for patent infringement was brought against Genpharm Inc. within the statutory forty-five day period.

However, the Act provides that approval of an abbreviated application that contains a certification described in section 505(j)(2)(A)(vii)(IV) (a "Paragraph IV Certification"), and that is for a drug product for which a previous abbreviated application has been submitted which also contains a Paragraph IV Certification, shall be made effective not earlier than one hundred and eighty days after:

(1) the date of the first commercial marketing of the drug under the previous application, or

(2) the date of a decision of a court holding the patent which is the subject of the certification to be invalid or not infringed, whichever occurs first [Section 505(j)(5)(B)(iv)].

An abbreviated application for Ticlopidine Hydrochloride Tablets, 250 mg, containing a Paragraph IV Certification was previously accepted for filing by this office prior to receipt of your application. Accordingly, your application will be eligible for final approval beginning on the date that is one hundred and eighty (180) days after the first commercial marketing of the drug under the previous application, or the date of a court decision described under section 505(j)(5)(B)(iv), whichever is earlier. We refer you to the Agency's recently issued guidance document "180-Day Generic Drug Exclusivity Under the Hatch-Waxman Amendments" (June 1998), for additional information.

Because the Agency is granting a tentative approval for this application, when your application may be considered for final approval, you must amend your application at least 60, but not more than 90 days prior to the date you believe the Agency may approve your application. This amendment should identify changes, if any, in the conditions under which the drug product was tentatively approved, and should include updated information such as final printed labeling, chemistry, manufacturing, and controls data as appropriate. Alternatively, an amendment should be submitted stating that no changes have been made to the application since the date of tentative approval. This submission should be designated as a MINOR Amendment in your cover letter. In addition to, or instead of, the amendment requested above, the Agency may, at any time prior to the final date of approval, request that you submit an amendment containing the information described above.

Any changes in the conditions outlined in this abbreviated application and the status of the manufacturing and testing facilities' compliance with current good manufacturing procedures are subject to Agency review before final approval of the application will be made.

In addition to, or instead of, the amendments referred to above, the Agency may, at any time prior to the final date of approval, request that you submit amendments containing the information requested above.

Failure to submit either or both amendments may result in rescission of this tentative approval determination, or delay in issuance of the final approval letter.

The drug product that is the subject of this abbreviated application may not be marketed without final Agency approval under section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug before the final approval date is prohibited under section 501 of the Act. Also, until the Agency issues the final approval letter, this drug product will not be listed in the Agency's "Approved Drug Products with Therapeutic Equivalence Evaluations" list.

Prior to submitting the amendment(s), please contact Kassandra Sherrod, Project Manager, at (301) 827-5849, for further instructions.

The introduction or delivery for introduction into interstate commerce of the drug before the effective approval date is prohibited under 21 U.S.C. 331(d).

Sincerely yours,

/S/ 1-28-99

Douglas L. Spörn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 75-161

Lipha Pharmaceuticals Inc.
U.S. Agent for: Genpharm Inc.
Attention: Anita M. Goodman, M.D.
9 West 57 th Street
Suite 3825
New York, NY 10019-2701

AUG 15 1997

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Ticlopidine HCl Tablets, 250 mg

DATE OF APPLICATION: July 8, 1997

DATE OF RECEIPT: July 11, 1997

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Kassandra Sherrod
Project Manager
(301) 827-5848

Sincerely yours,

/S/

8/14/97

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

GENPHARM

Office of Generic Drugs
Center for Drug Evaluation and Research
Food & Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA

Re: Abbreviated New Drug Application
Ticlopidine Hydrochloride Tablets
250 mg

We are pleased at this time to submit an original Abbreviated New Drug Application for our product - Ticlopidine Hydrochloride tablets, 250 mg.

The purpose of this application is to gain FDA approval to market Ticlopidine HCl tablets, 250 mg, in the U.S.A. The drug product described above is the same as Ticlid®, manufactured by Syntex Laboratories, Inc (which has been purchased by Hoffman-La Roche). We have submitted comparative information to indicate that our product is the same as the reference listed drug product. This information is presented in tabular form, comparing active ingredient, conditions of use, route of administration, dosage form, strength, bioavailability, and labeling for the products as supplied by Genpharm Inc. and by Syntex Laboratories, Inc.

We have enclosed one (1) archival, one (1) review, and one (1) field copy of the application in accordance with 21 CFR § 314.55. As required, three (3) additional separately bound copies of the analytical methods and descriptive information needed to perform the tests on the samples (both the bulk active ingredient and finished dosage form) are included as one of the volumes of the archival copy of this ANDA. The number of volumes in the archival, review and field copies of the ANDA are as follows:

Blue Archival Copy	7 volumes
Orange Review Copy	5 volumes
Red Review Copy	3 volumes
Burgundy Field Copy	3 volumes.

We certify that the Field Copy is a true copy of the technical section contained in the archival and review copies of this application and has been submitted to the Office of Generic Drugs.

GENPHARM INC. 85 ADVANCE ROAD • ETOBICOKE • ONTARIO • CANADA M8Z 2S9 • (416) 236-2631 • FAX (416) 236-2940 • TOLL FREE: 1-800-668-3174

In addition, for the Bioequivalence Section, we have enclosed a computer diskette with the analytical data and bioavailability parameters in the format prescribed by the FDA. A hard copy of the diskette data is also included in this section. The diskette and hard copy of the data is located in Section VI.1 of the Orange Review Copy of this application.

We trust the information submitted is sufficient for this Abbreviated New Drug Application to be evaluated. Although Dr. Anita M. Goodman is our U.S. agent, if there are any questions with respect to this application, please contact the undersigned either by direct written and/or by telephone communications. Genpharm can be contacted directly at 1-800-661-7134 and Dr. Anita M. Goodman can be reached at (212) 223-1282.

A letter of authorization, allowing Ms. Anita M. Goodman to act as our U.S. agent, is included in Section XX.2.a of this application.

We request that all information in this file be treated as confidential within the meaning of 21 CFR section 314.430 and that no information from the file be submitted to an applicant without our written consent to an authorized member of your Office.

Yours sincerely

for Richard Pike
Director, Regulatory Affairs
GENPHARM INC.

July 8/97
(date)

cc: Ms. Anita M. Goodman, M.D.
Executive Vice President & Chief Operating Officer
Lipha Pharmaceuticals, Inc.
9 West 57th St., Suite 3825
New York, NY 10019-2701

GENPHARM

BIOAVAILABILITY
ORIG AMENDMENT
N/AE
BIOEQUIVALENCY AMENDMENT

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II,
7500 Standish Place, Room 150
Rockville, Maryland 20855

RE: ANDA No. 75-161
TICLOPIDINE HCl TABLETS
250 mg

MAR 02 1998

Dear Sirs/Madam:

Please find enclosed a ***BIOEQUIVALENCY AMENDMENT*** to ANDA # 75-161 in response to the faxed letter dated January 8, 1998, from Nancy Chamberlin, Project Manager.

For the reviewers' convenience, we have:

a) attached a copy of the letter dated January 8, 1998;
b) formatted our amendment such that each comment made by the reviewer has been restated in *italic* print;
c) provided our response following the comment.

We have enclosed one (1) archival and one (1) review copy of the application in accordance with 21 CFR § 314.55. In each copy, a signed form FDA 356h by our US agent is submitted.

We trust the information submitted is sufficient for this amendment to be evaluated. Although Dr. Anita Goodman of Lipha Pharmaceuticals, Inc., New York, New York is our US Agent, should you have any questions, please contact the undersigned at 1-800-661-7134.

Thank you for your prompt handling of this submission.

Yours Sincerely,
Genpharm Inc.

R. K. Pike

Richard K. Pike
Director, Regulatory Affairs

RECEIVED
MAR 0 4 1998
GENERIC DRUGS

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NAT 1/13/98

NEW CORRESP

NC

GENPHARM

January 9, 1998

Office of Generic Drugs
Center for Drug Evaluation and Research
Food & Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ACKNOWLEDGEMENT

Re: Ticlopidine Tablets 250 mg (ANDA # 75-161)

We acknowledge receipt of the ***BIOEQUIVALENCY AMENDMENT*** letter, dated Jan. 8, 1998 from Ms. Nancy Chamberlin, project manager of the Office of Generic Drugs, CDER, FDA.

We are currently addressing the comments made by the reviewer and will file an amendment when the response is complete.

If there are any questions with respect to this application, you may direct written and telephoned communications to Genpharm at 1-800-661-7134 or you may contact our U.S. agent, Ms. Anita M. Goodman, at (212) 223-1282.

Yours sincerely

for Richard Pike
Director, Regulatory Affairs
GENPHARM INC.

Jan 9/98
(date)

cc: Ms. Anita M. Goodman, M.D.
Executive Vice President & Chief Operating Officer
Lipha Pharmaceuticals, Inc.
9 West 57th St., Suite 3825
New York, NY 10019-2701

RECEIVED
JAN 12 1998
GENERIC DRUGS

GENPHARM INC. 85 ADVANCE ROAD • ETOBICOKE • ONTARIO • CANADA M8Z 2S9 • (416) 236-2631 • FAX (416) 236-2940 • TOLL FREE: 1-800-668-3174

GENPHARM

ORIG AMENDMENT
N/AC

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II,
7500 Standish Place, Room 150
Rockville, Maryland 20855

MAJOR AMENDMENT

RE: ANDA No. 75-161
TICLOPIDINE HCl TABLETS
250 mg

Dear Sirs/Madam:

Please find enclosed a ***MAJOR AMENDMENT*** to ANDA # 75-161 in response to the faxed letter dated November 6, 1997, from Kassandra Sherrod, Project Manager.

For the reviewers' convenience, we have:

a) attached a copy of the letter dated Nov., 6, 1997;
b) formatted our amendment such that each comment made by the reviewer has been restated in *italic* print;
c) provided our response following the comment.

We have enclosed one (1) archival, one (1) review copy, and (1) field copy of the application in accordance with 21 CFR § 314.55. In each copy, a signed form FDA 356h by our US agent is submitted. We also certify that the Field Copy is a true copy of the technical section contained in the archival and review copies of this application and has been submitted to the Office of Generic Drugs.

Also enclosed in this amendment, we have provided documentation certifying that a notice that met the content requirement under paragraph (c) of 21 C.F.R. § 314.95 was provided to each person identified under paragraph (a) of this section. The copy of the return receipt and the receipt letter from the patent and the approved application holder for our certification of non-infringement of U.S. Patent 4,591,592 is provided.

We trust the information submitted is sufficient for this amendment to be evaluated. Although Dr. Anita Goodman of Lipha Pharmaceuticals, Inc., New York, New York is our US Agent, should you have any questions, please contact the undersigned at [illegible]4.

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APR 0 6 1998
GENERIC DRUGS

GENPHARM INC. 85 ADVANCE ROAD • ETOBICOKE • ONTARIO • CANADA M8Z 2S9 • (416) 236-2631 • FAX (416) 236-2940 • TOLL FREE: 1-800-668-3174

Thank you for your prompt handling of this submission.

Yours Sincerely,
Genpharm Inc.

Jo-Anne Richardeau

(for) Richard K. Pike
Director, Regulatory Affairs

GENPHARM

Telephone Amendment

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II,
7500 Standish Place, Room 150
Rockville, Maryland 20855

JAT NP

NEW COPY NC

MAY 06 1998

RE: ANDA No. 75-161
TICLOPIDINE HCl TABLETS
250 mg

Dear Sirs/Madam:

Pursuant to 21 CFR §314.95, Genharm Inc. ("Genpharm") submits this Amendment to ANDA #75-161 to

(1) document receipt of Genpharm's Notice of Paragraph IV Certification; and

(2) advise the Agency that the 45 day period described in 21 U.S.C. §335(j)(4)(B)(iii) has expired.

On February 13, 1998, our legal counsel, Frommer Lawrence & Haug LLP sent a Notice of Paragraph IV Certification to Syntex Laboratories, c/o Roche Holdings, Inc., the holder of the approved NDA for Ticlopidine Hydrochloride Tablets, 250 mg, and also to Syntex U.S.A. Inc., the owner of U.S. Patent No. 4,591,592, which is listed in the Orange Book. The Notice met the content requirements of 21 CFR §314.95(c). The Notice was sent by U.S. certified mail, return receipt requested to each person identified in 21 CFR §314.95(a).

Enclosed are copies of the original certified mail return receipts (which were previously submitted). They indicate that Syntex U.S.A. Inc. (The patent owner) received the Notice on February 20, 1998 and that Syntex Laboratories c/o Roche Holdings, Inc. (the NDA holder) received the Notice on February 27, 1998.

Please note that the 45-day period described in 21 CFR 314.95(f) and 21 U.S.C. §355(j)(4)(B)(iii) expired on April 13, 1998. No lawsuit was filed within the 45 day period against Genpharm for infringement of the listed patent. Therefore, Genpharm respectfully requests that approval of this application become effective on the date the FDA issues an approval letter.

... cont'd ...

5-18-98

If there any questions with respect to this application, you may direct written and telephone communications to Genpharm at 1-800-661-7134 or you may contact our U.S. agent, Dr. Anita M. Goodman of Lipha Pharmaceuticals, Inc. New York, New York, at (212) 223-1282.

Sincerely,
Genpharm Inc.

Ms. Tirtho Uppal
Director, Regulatory Affairs

Enclosures

GENPHARM

NAI
Copy of notification
Dt 5/11/98

NEW CORRESP
NC

APR 30 1998

Telephone Amendment

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II,
7500 Standish Place, Room 150
Rockville, Maryland 20855

RE: ANDA No. 75-161
TICLOPIDINE HCl TABLETS
250 mg

Dear Sirs/Madam:

In reply from a telephone request from Ms. Denise Huie, of FDA Generic Drugs (April 30, 98) with our US Agent., please find enclosed a Telephone Amendment to ANDA# 75-161.

Submitted in this amendment, we have provided a copy of the letter to Hoffman-LaRoche along with the return receipt as required in "paragraph IV" of the regulations.

We are submitting this Telephone Amendment by fax followed by a hard copy, one (1) archival copy. A signed form FDA 356h by our US agent will be provided in the Archival copy.

If there are any questions with respect to this application, you may direct written and telephone communications to Genpharm at 1-800-661-7134 or you may contact our U.S. agent, Dr. Anita M. Goodman of Lipha Pharmaceuticals, Inc. New York, New York, at (212) 223-1282.

Thank you for your prompt handling of this submission.

Yours Sincerely,
Genpharm Inc.

Ms. Tirtho Uppal
Director, Regulatory Affairs

RECEIVED
MAY 04 1998
GENERIC DRUGS

May 5 1998

GENPHARM INC. 85 ADVANCE ROAD • ETOBICOKE • ONTARIO • CANADA M8Z 2S9 • (416) 236-2631 • FAX (416) 236-2940 • TOLL FREE: 1-800-668-3174

GENPHARM

ORIG AMENDMENT
N/Amt

Office of Generic Drugs
Center for Drug Evaluation and Research
Food & Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MINOR AMENDMENT
For Final Approval

Re: ANDA #75-161
Ticlopidine HCl Tablets
250 mg

This **Minor Amendment** to our abbreviated new drug application is in response to the tentatively approved letter, dated January 28, 1999, from Douglas L. Sporn, Director, Office of Generic Drugs.

We are amending our application to identify and provide documents reflecting the changes made in the conditions under which the drug product was tentatively approved.

We have enclosed one (1) archival, one (1) review and one (1) field copy of the application in accordance with 21 CFR § 314.54. We certify that the Field Copy is a true copy of the technical section contained in the archival and review copies of this application and has been submitted to the Office of Generic Drugs.

We trust the information submitted is sufficient for this amendment to be evaluated. If there are any questions with respect to this application, you may direct written and telephoned communications to Genpharm directly at 1-800-661-7134 or you may contact our U.S. agent, Mr. Robert A. Femia, at (914) 425-7100.

Yours sincerely

Tirtho Uppal

Mrs. Tirtho Uppal
Director, Regulatory Affairs
GENPHARM INC.

8/18/99
(date)

cc: Mr. Robert A. Femia, PhD.
Vice President, Scientific & Regulatory Affairs
Par Pharmaceutical, Inc.
One Ram Ridge Road,
Spring Valley, NY
USA 10977

CENTER FOR DRUG EVALUATION AND RESEARCH
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AUG 19 1999
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GENPHARM

Office of Generic Drugs
Center for Drug Evaluation and Research
Food & Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

LABELLING AMENDMENT

ORIG AMENDMENT
AF

Re: ANDA #75-161
Ticlopidine HCl Tablets
250 mg

This **Labelling Amendment** to our abbreviated new drug application is in response to Koung Lee's telephone conversation followed by a fax on August 5, 1999.

We are amending our application to update the insert labelling to reflect the recently approved changes in the innovator's (Roche) insert, as requested by FDA. A side-by-side comparison of the most recently submitted insert to the revised insert has been included in this amendment. Twelve (12) copies of the final printed labelling material (package insert) are included in the submission package.

We have enclosed one (1) archival and one (1) review copy of the application in accordance with 21 CFR § 314.96.

We trust the information submitted is sufficient for this amendment to be evaluated. If there are any questions with respect to this application, you may direct written and telephoned communications to Genpharm directly at 1-416-207-1216 or you may contact our U.S. agent, Mr. Robert A. Femia, at (914) 425-7100.

Yours sincerely

Mrs. Tirtho Uppal
Director, Regulatory Affairs
GENPHARM INC.

Aug 13/99
(date)

CENTER FOR DRUG
REC'D
AUG 17 1999
OGD
EVALUATION AND RESEARCH

cc: Mr. Robert A. Femia, PhD.
Vice President, Scientific & Regulatory Affairs
Par Pharmaceutical, Inc.
One Ram Ridge Road,
Spring Valley, NY
USA 10977

ARCHIVAL COPY

GENPHARM

July 28, 1999

NEW CORRESP

NC

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

Re: ANDA No. 75-161 for Ticlopidine Hydrochloride

Dear Sir or Madam:

On January 28, 1999 the FDA notified Genpharm that its ANDA No. 75-161 for ticlopidine hydrochloride was tentatively approved subject to expiration of a 180-day exclusivity period under FDCA §505(j)(5)(B)(iv). As the FDA interpreted the statute at that time, the 180-day exclusivity period would not begin until the first-filed ANDA applicant began commercial marketing. Genpharm understands that the first-filed ticlopidine ANDA belongs to TorPharm, who began marketing ticlopidine earlier this month.

On July 20, 1999 the United States Court of Appeals for the District of Columbia Circuit in the case of *Teva Pharmaceuticals USA, Inc. v. FDA* __ F.3d __, 1999 WL 50659 (C.C.Cir. July 20, 1999), addressed the FDA's calculation of TorPharms's exclusivity period under the FDCA. Consistent with the Teva decision, the 180-day exclusivity period awarded to TorPharm-- which has barred FDA's approval of Genpharm's ANDA for ticlopidine—has expired. Further, on July 26 the D.C. Circuit court issued a formal mandate to the District Court to proceed in accordance with its decision.

The Court held that the FDA's interpretation of the statutory exclusivity period was arbitrary and capricious because it failed to recognize the August 14, 1998 dismissal of an action between Teva and Syntex in the U.S. District court for the Central District of California as a "court decision" trigger to begin the 180-day exclusivity period. Accordingly, the exclusivity period expired on February 10, 1999, not 180 days from the first commercial marketing by TorPharm. Since that date was passed, immediate effective approval of ANDA No. 75-161 is warranted and hereby requested.

Very truly yours,

Richard K. Pike
Senior Vice President
Research & Development and Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
AUG 02 1999
OGD

cc Liz Dickinson
Kassandra Sherrod

8-4-99

GENPHARM INC. 85 ADVANCE ROAD • ETOBICOKE • ONTARIO • CANADA M8Z 2S9 • (416) 236-2631 • FAX (416) 236-2940 • TOLL FREE: 1-800-668-3174

GENPHARM

ARCHIVAL COPY

ANDA 75-161

NEW CORRESP
NC

July 28, 1999

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II,
7500 Standish Place, Room 150
Rockville, Maryland 20855

GENERAL CORRESPONDENCE TO FILE

RE: **Educational Program for Ticlopidine Hydrochloride Tablets, 250 mg**

Dear Sir/Madam:

In a telephone discussion on July 27, 1999 between Mr. Kuong Lee, Labeling Division and Par Pharmaceutical Inc., our US agent, Mr. Kuong Lee requested that Genpharm submit to file a commitment to provide the post marketing program for review at the time of marketing.

In response to the request, Genpharm hereby commits to provide the post marketing program as proposed in our letter dated June 25, 1999 for review at time of marketing.

We have enclosed one (1) archival and one (1) review copy of this correspondence in accordance with 21 CFR § 314.54. In each copy, a signed form FDA 356h by our US agent is submitted. We will also be faxing a desk copy to the attention Mr. Kuong Lee, Labelling Reviewer.

Should you have any questions, please contact the undersigned at 1-800-661-7134 or you may contact our U.S. Agent, Mr. Robert A. Femia of Par Pharmaceutical Inc. at (914)-425-7100.

Sincerely yours,

Mrs. Tirtho Uppal
Regulatory Affairs, Director

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
AUG 02 1999
CGD

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Archival Copy

GENPHARM

NDA ORIG AMENDMENT

Office of Generic Drugs
Center for Drug Evaluation and Research
Food & Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

LABELING AMENDMENT

November 11, 1998

Re: Labeling Amendment to ANDA #75-161
Ticlopidine HCl Tablets
250 mg

This **Labeling Amendment** to our abbreviated new drug application is in response to Mr. Chan Park's telephone conversation followed with a fax letter dated October 15, 1998.

For the reviewers' convenience, the comments raised in the telephone conversation are presented in **bold** print and is followed by our response.

We have enclosed one (1) archival, and one (1) review copy of the application in accordance with 21 CFR § 314.55.

We trust the information submitted is sufficient for this amendment to be evaluated. If there are any questions with respect to this application, you may direct written and telephoned communications to Genpharm at 1-800-661-7134 or you may contact our U.S. agent, Mr. Robert A. Femia of Par Pharmaceutical, Inc. at (914)-425-7100.

Yours sincerely

Mrs. Tirtho Uppal
Director, Regulatory Affairs
GENPHARM INC.

Nov 11/98
date

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NEW CORRESP

NC

GENPHARM

October 1, 1998

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

AMENDMENT
CORRESPONDENCE TO FILE

Re: Ticlopidine Tablets, 250 mg (ANDA # 75-161)

Dear Sirs;

This is to advise of that the following representative/firm has been appointed as Genpharm's US agent for the above mentioned ANDA.

Robert A. Femia, PhD
Vice-President, Scientific & Regulatory Affairs
Par Pharmaceutical Inc.
One Ram Ridge Road
Spring Valley
New York 10977

The telephone numbers are:

Telephone No. (914) 425-7100 extension 708
Fax No. (914) 425-7907

We have enclosed one (1) archival, one (1) review and one (1) field copy of the application in accordance with 21 CFR § 314.55. We certify that the Field Copy is a true copy of the review copy of this application and has been submitted to the Office of Generic Drugs.

Should you have any questions, please do not hesitate to contact the undersigned at 1-800-661-7134

Sincerely yours,
Genpharm Inc.

Tirtho Uppal
Director, Regulatory Affairs

OCT 0 6 1998

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FPL ORIG AMENDMENT N/AM

1 of 3 rcvd 9/24/98

GENPHARM

September 22, 1998

Office of Generic Drugs, CDER, FDA

Document Control Room
Metro Park North II,
7500 Standish Place, Room 150
Rockville, Maryland 20855

MINOR AMENDMENT

RE: ANDA No. ~~76-161~~ 75/61
TICLOPIDINE TABLETS
250 MG

Dear Sirs/Madam:

This *MINOR AMENDMENT* to our ANDA #75-161 is in response to your faxed letter, dated September 9, 1998 from Dr. Frank O. Holcombe Jr. Director of the Division of Chemistry II. Our response to the Labelling Deficiency letter dated August 11, 1998 from Mr. Jerry Philips, is also enclosed.

For the reviewers' convenience, we have:

a) attached a copy of the letters dated September 9, 1998 and August 11, 1998.
b) formatted our amendment such that each comment made by the reviewer has been restated;
c) provided our response following the comment.

We have enclosed one Archival; one Chemistry Review; one Bioequivalence Section, and one Field copy of the application in accordance with 21 CFR § 314.55. We certify that the Field Copy is a true copy of the technical section contained in the Archival and Chemistry Review copies of this application and have been submitted to the Office of Generic Drugs. Along with our response, a signed form FDA 356h by our US agent, Dr. Anita Goodman of Lipha Pharmaceuticals, Inc., New York, N.Y., is submitted.

We trust the information submitted is sufficient for this amendment to be evaluated. If there are any questions with respect to this application, you may direct written and telephoned communications to Genpharm Inc. at 1-800-661-7134 or you may contact our US agent, Dr. Anita Goodman, at (212) 398-4602.

Thank you for your prompt handling of this submission.

Yours Sincerely,
Genpharm Inc.

Mrs. Tirtho Uppal
Director, Regulatory Affairs

RECEIVED
SEP 24 1998
GENERIC DRUGS

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