CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 75-253

CORRESPONDENCE

A Trusted Name For Over Half A Century

PUREPAC

ORIGINAL

Purepac Pharmaceutical Co.
200 Elmora Avenue, Elizabeth, New Jersey 07207
908-527-9100
Fax: 908-527-0649

UPS OVERNIGHT COURIER

August 9, 1999

Mr. Douglas Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation & Research
Food & Drug Administration
Document Control Room
MPN II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 75-253, Ticlopidine Hydrochloride Tablets, 250 mg

Dear Mr. Sporn:

Reference is made to our tentatively approved Abbreviated New Drug Application for Ticlopidine Hydrochloride Tablets, ANDA #75-253. Further reference is made to your telephone request of August 5, 1999 between Teresa Wang from the FDA and the undersigned.

Purepac Pharmaceutical Co. is amending the above referenced application to provide for revised package insert labeling as per your request of August 5, 1999.

Enclosed please find twelve (12) copies of the revised insert for your review. Also enclosed is a side-by-side comparison of our proposed insert and last revised insert with all differences annotated and explained. If this meets with your approval, please consider this as final printed insert labeling.

Purepac Pharmaceutical Co. looks forward to your approval of this Abbreviated New Drug Application.

Sincerely,

PUREPAC PHARMACEUTICAL CO.

Joan Janulis, R.A.C.
Vice President, Regulatory Affairs

JJ/cs

Enclosures

A Trusted Name For Over Half A Century

PUREPAC

Purepac Pharmaceutical Co.
200 Elmora Avenue, Elizabeth, New Jersey 07207
908-527-9100
Fax: 908-527-0649

TELEPHONE AMENDMENT

NAI 8/6/99
NEW CORRESP
NC

UPS OVERNIGHT COURIER

July 28, 1999

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

RE: ANDA 75-253, Ticlopidine Hydrochloride Tablets, 250 mg

Dear Mr. Sporn:

Reference is made to a telephone conversation between me and Mr. Koung Lee of the Labeling Review Branch on July 27, 1999.

During this conversation, Mr. Lee confirmed that our proposed educational program which was submitted to the agency on June 18, 1999, has been deemed satisfactory, and requested a letter of commitment regarding submission of printed educational materials upon initial marketing of our product. Pursuant to Mr. Lee's request, we present the following:

Purepac Pharmaceutical Co. hereby commits to submitting printed copies of the materials from our educational program (detailed in our submission of June 18, 1999) to the Office of Generic Drugs upon initial marketing of Ticlopidine Hydrochloride Tablets, 250 mg.

We trust that this Telephone Amendment addresses all remaining issues related to this application and we look forward to final ANDA approval.

If you have any questions regarding this submission, please contact the undersigned at (908) 659-2430.

Sincerely,

PUREPAC PHARMACEUTICAL CO.

Joan Janulis, R.A.C.
Vice President, Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUL 29 1999
OGD

NAI 8/3,

ORIGINAL

A Trusted Name For Over Half A Century

PUREPAC

Purepac Pharmaceutical Co.
200 Elmora Avenue, Elizabeth, New Jersey 07207
908-527-9100
Fax: 908-527-0649

AMENDMENT - Request for Final Approval

UPS OVERNIGHT COURIER

July 22, 1999

NEW CORRESP.

NC

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

RE: ANDA 75-253, Ticlopidine Hydrochloride Tablets, 250 mg
Request for Final Approval

Dear Mr. Sporn:

Purepac Pharmaceutical Co. hereby requests that the agency issue a letter of final approval with an immediate effective date for the referenced Abbreviated New Drug Application. The basis for our request is as follows:

1. All requirements for final approval of the abbreviated application have been satisfied.

In this regard, please note the following:

- A Minor Amendment, updating chemistry, manufacturing and controls information, was submitted on April 29, 1999. This submission was made in accordance with the request contained in the agency's July 15, 1998 letter stating that the application is tentatively approved.
- In response to the agency's June 15, 1999 letter, Purepac submitted our proposed educational program for Ticlopidine Hydrochloride Tablets on June 18, 1999. Furthermore, Purepac contacted Mr. Adolph Vezza of the Labeling Review Branch on July 13, 1999 regarding the status of the review of our proposed educational material. Mr. Vezza informed us that Dr. Mary Fanning, reviewer for this material, stated the educational material is acceptable at this time.

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JUL 23 1999
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Faulding Inc Purepac Pharmaceutical Co. is a subsidiary of Faulding Inc.

Nadeem 7.26.99

2. Torpharm's generic exclusivity has expired and Purepac is entitled to final approval.

On July 20, 1999, the U.S. Court of Appeals for the District of Columbia Circuit ruled that the dismissal of Teva's lawsuit against Hoffman LaRoche triggered TorPharm's 180-day exclusivity for ticlopidine. Teva Pharmaceuticals, USA, Inc. v. U.S. Food and Drug Administration, Nos. 99-5022, 99-5027 (D.C. Cir. July 20, 1999). A copy of the Court's decision is attached. Purepac was a party in this lawsuit on the side of Teva. The effect of the appellate Court's ruling in Teva is that TorPharm's exclusivity expired on February 10, 1999, 180 days after Teva's declaratory judgment petition was dismissed because the patent holder conceded that Teva's product did not infringe the patent at issue.

Based upon the Court's decision in Teva, Purepac requests that FDA immediately approve Purepac's ANDA for ticlopidine. The Court in Teva ruled that the 180 days of exclusivity has expired for TorPharm (the first paragraph IV applicant) and nothing in the Court's decision prevents FDA from acting now to approve additional ANDAs. The Court also found that "Teva and Purepac face continued harm because of their denied access to the market." Slip op. at 16, n.8. Once the 180-days of exclusivity has expired, the FDA *is required* by statute (§ 505(j)(5)(D)(iv)) to approve all tentatively approved ANDAs immediately. Because Purepac has a tentative approval, Purepac is entitled to an immediate final approval.

We trust that you will find the information contained in this Amendment complete and in order and look forward to the final approval of our Abbreviated New Drug Application.

If you have any questions regarding this submission, please contact the undersigned at (908) 659-2430.

Sincerely,

PUREPAC PHARMACEUTICAL CO.

Elizabeth Trowbridge / for

Joan Janulis, R.A.C.
Vice President, Regulatory Affairs

A Trusted Name For Over Half A Century

PUREPAC

ORIGINAL

Purepac Pharmaceutical Co.
200 Elmora Avenue, Elizabeth, New Jersey 07207
908-527-9100
Fax: 908-527-0649

Noted. To Charlie Hoppes FYI
M. Anderson 6/23/99
7/12/99 Educational program is acceptable
Mary
HFD-CDRES
NC

June 18, 1999

Mr. Douglas Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation & Research
Food & Drug Administration
Document Control Room
MPN II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 75-253, Ticlopidine Hydrochloride Tablets, 250 mg
Educational Program for Safe Use of the Drug Product

Dear Mr. Sporn:

This letter responds to your June 15, 1999 correspondence requesting that Purepac define our intentions with respect to the implementation of an educational program to promote the safe use of Ticlopidine Hydrochloride Tablets. Your letter indicated that the holder of the application for the reference listed drug, Ticlid® provides educational programs for health care professionals, along with a gratuitous CBC monitoring program to detect the early signs of potential life-threatening hematological side effects (neutropenia/agranulocytosis and thrombocytopenic purpura). Please be advised that Purepac intends to engage in a program to disseminate information regarding the safe use of Ticlopidine Hydrochloride Tablets. At this point in time, we have no intentions of providing a gratuitous CBC monitoring program.

Our proposed educational program is comprised of two basic elements: 1) An educational brochure and 2) A journal ad. **Attachment 1** of this correspondence defines, in details, the specific provisions of our program, including the means of dissemination for the associated literature, the targeted population, and the frequency of dissemination. **Attachment 2** contains a copy of our educational brochure and **Attachment 3** contains a copy of our journal ad. Please note that these articles encompass the recommended characteristics for an effective educational program as defined in your June 15, 1999 correspondence.

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JUN 21 1999
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EVALUATION AND RESEARCH

NLL 6-22-99

We trust that our commitment to commence this program upon initial commercial distribution of our product will remove any barrier to final ANDA approval presently imposed by the pending Citizen Petition.

If you have any questions regarding the information contained in this correspondence, please do not hesitate to contact the undersigned at (908) 659-2430.

Sincerely,

PUREPAC PHARMACEUTICAL CO.

Joan Janulis, R.A.C.
Vice President, Regulatory Affairs

JJ/cs

Enclosures

ANDA 75-253

Purepac Pharmaceutical Co.
Attention: Joan Janulis
200 Elmora Avenue
Elizabeth, New Jersey 07207

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 (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

A Trusted Name For Over Half A Century

PUREPAC

ORIGINAL

Purepac Pharmaceutical Co.
200 Elmora Avenue, Elizabeth, New Jersey 07207
Tel. 908-527-0600
Fax. 908-527-0649

UPS OVERNIGHT COURIER

MINOR AMENDMENT FOR FINAL ANDA APPROVAL

April 29, 1999

Mr. Douglas Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

5/4/99
Refer to my E-Mail of this date to Robert Lust

RE: ANDA #75-253, Ticlopidine Hydrochloride Tablets, 250mg

Dear Mr. Sporn:

Reference is made to our November 14, 1997 submission of an Abbreviated New Drug Application for Ticlopidine Hydrochloride Tablets, 250 mg, ANDA #75-253. Further reference is made to your July 15, 1998 letter stating that this application is tentatively approved.

In accordance with the request contained in the July 15, 1998 correspondence, Purepac is hereby submitting this Minor Amendment containing updated chemistry, manufacturing and controls (CMC) information. The specific modifications incorporated into the revised documents are explained in the appropriate section of this submission. In addition to the CMC information contained in the amendment, please note the following changes, which took place subsequent to the granting of tentative ANDA approval:

- Final printed inserts, revised in accordance with the agency's July 29, 1998 facsimile, were submitted as an amendment to this application on August 11, 1998. No further labeling changes have been implemented.
- An amendment requesting approval for an alternative source of the active pharmaceutical ingredient was submitted on March 30, 1999. **This amendment was withdrawn on April 28, 1999.**

Please note that, Section 2 of this amendment contains the required Field Copy Certification.

CENTER FOR DRUG EVALUATION AND RESEARCH
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APR 30 1999
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5-4-99

This completes our Minor Amendment summarizing all changes to the application's provisions following tentative approval. We trust that you will find this submission complete and in order and look forward to the final approval of ANDA #75-253. If you have any questions regarding this submission, please do not hesitate to call the undersigned at (908) 659-2430.

Sincerely,
PUREPAC PHARMACEUTICAL CO.

Elizabeth Trombridge (for)

Joan Janulis, R.A.C.
Vice President, Regulatory Affairs

JJ:cch
Enclosures

A Trusted Name For Over Half A Century
PUREPAC

Purepac Pharmaceutical Co.
200 Elmora Avenue, Elizabeth, New Jersey 07207
908-527-9100
Fax: 908-527-0649

Noted. NAI 3/30/99 ORIGINAL
the piece is being converted to an "A A" (it is not a response to an TA letter) 5/3/99

WITHDRAWAL OF MINOR AMENDMENT

UPS OVERNIGHT COURIER

April 28, 1999 NEW CORRESP

Mr. Douglas Sporn, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NC

RE: ANDA #75-253, TICLOPIDINE HYDROCHLORIDE TABLETS, 250 MG

Dear Mr. Sporn:

Purepac Pharmaceutical Co. hereby requests the withdrawal of the March 30, 1999 Minor Amendment to our tentatively approved application for Ticlopidine Hydrochloride Tablets, 250 mg. The referenced amendment provided for
as an alternate source of the active pharmaceutical ingredient.

If you have any questions regarding this submission, please do not hesitate to contact the undersigned at (908) 659-2430.

Sincerely,

PUREPAC PHARMACEUTICAL CO.

Elizabeth M Trowbridge /for
Joan Janulis, R.A.C.
Vice President, Regulatory Affairs

Attachments

RECEIVED

GENERIC DRUGS

Madeline 4-30-99