CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 75-326

ADMINISTRATIVE

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-326 Date of Submission: July 30, 1998

Applicant's Name: Eon Labs Manufacturing, Inc.

Established Name: Ticlopidine Hydrochloride Tablets, 250 mg

Labeling Deficiencies:

1. CONTAINER (30's, 60's, & 500's)

   Satisfactory

2. INSERT

   a. GENERAL

      i. Please use a minimum 4 point font throughout your insert labeling, including in your figures.

      ii. We encourage you to relocate "**Rx only**" to the TITLE section.

      iii. Revise the BOXED WARNING section as follows and relocate between the TITLE and DESCRIPTION sections.

      WARNING: Ticlopidine hydrochloride tablets can cause life-threatening hematological adverse reactions, including neutropenia/agranulocytosis and thrombotic thrombocytopenic purpura (TTP).

      ***Neutropenia/Agranulocytosis*: Among 2048 patients in clinical trials, there were 50 cases (2.4%) of neutropenia (less than 1200 neutrophils/mm^3), and the neutrophil count was below 450/mm^3 in 17 of these patients (0.8% of the total population).**

      ***TTP*: Thrombotic thrombocytopenic purpura was not seen during clinical trials, but US physicians reported about 100 cases between 1992 and 1997. Based on an estimated patient exposure of 2 million to 4 million, and assuming an event reporting rate of 10% (the true rate is not known), the incidence of ticlopidine-associated TTP may be as high as one case in every 2000 to 4000 patients exposed.**

***Monitoring of Clinical and Hematologic Status*: Severe hematological adverse reactions may occur within a few days of the start of therapy. This incidence of TTP peaks after about 3 to 4 weeks of therapy and neutropenia peaks at approximately 4 to 6 weeks with both declining thereafter. Only a few cases have arisen after more than 3 months of treatment.**

Hematological adverse reactions cannot be reliably predicted by any identified demographic or clinical characteristics. During the first 3 months of treatment, patients receiving ticlopidine hydrochloride tablets must, therefore, be hematologically and clinically monitored for evidence of neutropenia or TTP. If any such evidence is seen, ticlopidine hydrochloride tablets should be immediately discontinued.

The detection and treatment of ticlopidine-associated hematological adverse reactions are further described under WARNINGS.

b. CLINICAL PHARMACOLOGY

i. Pharmacokinetics and Metabolism

Start a new paragraph beginning with the fourth sentence of the first paragraph.

ii. Renally Impaired Patients

Start a new paragraph beginning with the third sentence and add "%" after "28" and "37".

c. CLINICAL TRIALS

i. Add the word "years" after "2" in the second sentence.

ii. In the "TASS - Fatal or Nonfatal Stroke" graph, add "10" to the y-axis.

d. INDICATIONS AND USAGE

Delete the second sentence and add the following paragraph.

Because ticlopidine is associated with a risk of life-threatening blood dyscrasias including thrombotic thrombocytopenic purpura (TTP) and

neutropenia/agranulocytosis (see BOXED WARNING and WARNINGS), ticlopidine should be reserved for patients who are intolerant or allergic to aspirin therapy or who have failed aspirin therapy.

e. CONTRAINDICATIONS - First sentence:

The second bullet should read as follows.

- Presence of hematopoietic disorders such as neutropenia and thrombocytopenia or a past history of TTP

f. WARNINGS

Delete the BOXED WARNING and the first paragraph and add the following.

WARNINGS: ***Hematological Adverse Reactions:*** *Neutropenia*: Neutropenia may occur suddenly. Bone-marrow examination typically shows a reduction in myeloid precursors. After withdrawal of ticlopidine, the neutrophil count usually rises to >1200/mm^3 within 1 to 3 weeks.

Thrombocytopenia: Rarely, thrombocytopenia may occur in isolation or together with neutropenia.

Thrombotic Thrombocytopenic Purpura (TTP): TTP is characterized by thrombocytopenia, microangiopathic hemolytic anemia (schistocytes [fragmented RBCs] seen on peripheral smear), neurological findings, renal dysfunction, and fever. The signs and symptoms can occur in any order; in particular, clinical symptoms may precede laboratory findings by hours or days. With **prompt** treatment (often including plasmapheresis), 70% to 80% of patients will survive with minimal or no sequelae. Because platelet transfusions may accelerate thrombosis in patients with TTP on ticlopidine, they should, if possible, be avoided.

Monitoring for Hematologic Adverse Reactions: Starting just before initiating treatment and continuing through the third month of therapy, patients receiving ticlopidine must be monitored every 2 weeks. Because of ticlopidine's long plasma half-life, patients who discontinue ticlopidine during this 3-month period should continue to be monitored for 2 weeks after discontinuation. More frequent monitoring, and monitoring after the first 3 months of therapy, is necessary only in patients with clinical signs (eg, signs or symptoms suggestive of infection) or laboratory signs (eg, neutrophil count less than 70% of the baseline count, decrease in hematocrit or platelet count) that suggest incipient hematological adverse reactions.

Clinically, fever might suggest either neutropenia or TTP; TTP might also be suggested by weakness, pallor, petechiae or purpura, dark urine (due to blood, bile pigments, or

hemoglobin) or jaundice, or neurological changes. Patients should be told to discontinue ticlopidine and to contact the physician immediately upon the occurrence of any of these findings.

Laboratory monitoring should include a complete blood count, with special attention to the absolute neutrophil count (WBC X % neutrophils), platelet count, and the appearance of the peripheral smear. Ticlopidine is occasionally associated with trombocytopenia unrelated to TTP. Any acute, unexplained reduction in **hemoglobin** or platelet count should prompt further investigation for a diagnosis of TTP, and the appearance of **schistocytes** (fragmented RBCs) on the smear should be treated as presumptive evidence of TTP. If there are laboratory signs of TTP, or if the neutrophil count is confirmed to be $<1200/mm^3$, then the drug should be discontinued.

g. PRECAUTIONS

i. Replace the last sentence of the second paragraph with:

Because platelet transfusions may accelerate thrombosis in patients with TTP on ticlopidine, they should, if possible, be avoided.

ii. Use in Renally Impaired Patients

Delete the coma between "…discontinue it altogether" and "if hemorrhagic or hematopoietic…"

iii. Information for the Patient (See PPI)

A). Replace the entire first paragraph with the following.

Patients should be told that a decrease in the number of white blood cells (neutropenia) or platelets (thrombocytopenia) can occur with ticlopidine, especially during the first 3 months of treatment and that neutropenia, if it is severe, can result in an increased risk of infection. They should be told it is critically important to obtain the scheduled blood tests to detect neutropenia or thrombocytopenia. Patients should also be reminded to contact their physicians if they experience any indication of infection such as fever, chills, or sore throat, any of which might be a consequence of neutropenia. Thrombocytopenia may be part of a syndrome called TTP. Symptoms and signs of TTP, such as fever, weakness, difficulty speaking, seizures, yellowing of skin or eyes, dark or

bloody urine, pallor or petechiae (pinpoint hemorrhagic spots on the skin), should be reported immediately.

B). Replace "report promptly" with "promptly report" in the last sentence of the third paragraph.

iv. Drug Interactions

Add a space between "…resulted in an" and "18% decrease in…" in the eighth sentence.

v. Carcinogenesis, Mutagenesis and Impairment of Fertility

A). Put a space between "…of up to" and "100 mg/kg…" in the first sentence of the first paragraph.

B). Replace the last paragraph with the following.

Ticlopidine was not mutagenic *in vitro* in the Ames test, the rat hepatocyte DNA-repair assay, or the Chinese-hamster fibroblast chromosomal aberration test; or *in vivo* in the mouse spermatozoid morphology test, the Chinese-hamster micronucleus test, or the Chinese-hamster bone-marrow-cell sister-chromatid exchange test. Ticlopidine was found to have no effect on fertility of male and female rats at oral doses up to 400 mg/kg/day.

vi. Pediatric Use

Replace the sentence with the following.

Safety and effectiveness in pediatric patients have not been established.

h. ADVERSE REACTIONS

i. Relocate the heading, "Percent of Patients with Adverse Events in Controlled Studies", within the top portion of the table.

ii. Hematological

Replace the sentence with the following.

Neutropenia/thrombocytopenia, TTP (see BOXED WARNING and WARNINGS), agranulocytosis, eosinophilia,

pancytopenia, thrombocytosis and bone-marrow depression have been reported.

iii. Hemorrhagic

Start a new paragraph beginning with third sentence.

iv. In the last paragraph of the section, delete "thrombotic thrombocytopenic purpura (TTP)" from the list of "…rarer, relatively serious events…".

i. OVERDOSAGE

i. Delete the hyphen between "600" and "mg" in the second sentence.

ii. Start a new paragraph beginning with the fifth sentence.

j. IMPORTANT INFORMATION ABOUT TICLOPIDINE HYDROCHLORIDE TABLETS

i. Replace the word "sheet" with "leaflet" in the fourth sentence of the first paragraph.

ii. Special Warning for Users of Ticlopidine Hydrochloride Tablets/Necessary Blood Tests

Replace the entire subsection with the following.

Ticlopidine is recommended to help reduce your risk of having a stroke, but only for patients who have had a stroke or early stroke warning symptoms while on aspirin, or for those who have these symptoms but are intolerant or allergic to aspirin.

Ticlopidine is not prescribed for those who can take aspirin to prevent a stroke because ticlopidine can cause life-threatening blood problems. **Getting your blood tests done and reporting symptoms to your doctor as soon as possible can avoid serious complications.**

The white cells of the blood that fight infection may drop to dangerous levels (a condition called neutropenia). This occurs in about 2.4% (1 in 40) of people on ticlopidine. You should be on the lookout for signs of infection such as fever, chills or sore throat. If this problem is caught early, it can almost always be reversed, but if undetected it can be fatal.

Another problem that has occurred in some patients taking ticlopidine is a decrease in cells called

platelets (a condition called thrombocytopenia). This may occur as part of a syndrome that includes injury to red blood cells, causing anemia, kidney abnormalities, neurologic changes and fever. This condition is called TTP and can be fatal.

Things you should watch for as possible early signs of TTP are yellow skin or eye color, pinpoint dots (rash) on the skin, pale color, fever, weakness on a side of the body, or dark urine. **If any of these occur, contact your doctor immediately.**

Both complicaitons occur most frequently in the first 90 days after ticlopidine is started. To make sure you don't develop either of these problems, your doctor will arrange for you to have your blood tested before you start taking ticlopidine and then every 2 weeks for the first 3 months you are on ticlopidine. If detected, neutropenia and thrombocytopenia can almost always be reversed. It is essential that you keep your appointments for the blood tests and that you call your doctor immediately if you have any indication that you may have TTP or neutropenia. If you stop taking ticlopidine for any reason within the first 3 months, you will still need to have your blood tested for an additional 2 weeks after you have stopped taking ticlopidine.

iii. Other Warnings and Precautions

A). Replace the last sentence with "These symptoms should be reported to your physician promptly."

B). Start a new paragraph beginning with the sentence "Some people may...or intestinal discomfort."

iv. After the "Other Warning and Precautions" subsection, add the following in bold face print.

If any of the symptoms described above for neutropenia, TTP or jaundice occur, contact your doctor immediately.

v. Replace the paragraph that precedes the "How Ticlopidine Works" subsection with the following.

It may take longer than usual to stop bleeding when taking ticlopidine. Tell your doctor if you have any more bleeding or bruising than usual, and, if you have emergency surgery, be sure to let your doctor or dentist know that you are taking ticlopidine. Also, tell your doctor well in advance of any planned surgery (including tooth extraction), because he or she may

recommend that you stop taking ticlopidine temporarily.

vi. Who Should Not Take Ticlopidine Hydrochloride Tablets?

Add as the third bullet the following.

- you have previously been told you had TTP

4. PATIENT PACKAGE INSERT (PPI)

a. Describe your plans for supplying the PPI with your product, e.g., how many inserts you will supply for each container size and how these inserts will be supplied.

b. Refer to the comment (j) under INSERT.

Please revise your package insert and patient package insert labeling, as instructed above, and submit four draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other factors (print size, prominence, etc.) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with the last submitted labeling with all differences annotated and explained.

/S/

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

RECORD OF TELEPHONE CONVERSATION

K. Sherrod, R. Rajagopalan and B. Arnwine talked to Sadie and went over each question on the second major deficiency. Sadie objected to each one of them and she was asked to respond to them. She said she will also talk to F. Fang.

DATE
March 1, 1999

ANDA NUMBER
ANDA 75-326

IND NUMBER

TELECON

INITIATED BY **MADE**

_ **APPLICANT/ SPONSOR** **BY TELE.**

X **FDA** _ **IN PERSON**

PRODUCT NAME
Ticlopidine HCl Tablets, 250 mg

FIRM NAME
Eon Labs

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD

Sadie Ciganek
Vice President, Reg. Affairs

TELEPHONE NUMBER
(718) 276-8600

SIGNATURE

/S/

3/15/99

Updated by A.S. of 8/12/99 (5-1)

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

/S/

ANDA Number: **75-326** Date of Submission: **April 27, 1999**

Applicant's Name: **Eon Labs Manufacturing, Inc.**

Established Name: **Ticlopidine Hydrochloride Tablets, 250 mg**

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: 30s, 60s, 500s
Satisfactory in FPL as of July 30, 1998 submission.

Professional Package Insert Labeling:
Satisfactory in FPL as of April 27, 1999 submission.

Revisions needed post-approval: None

NOTE: Before final approval, please confirm that the firm's educational plan is acceptable to Dr. Mary Fanning.

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356 (h) form: Ticlid Tablets

NDA Number:

NDA Drug Name: Ticlid Tablets

NDA Firm: Roche Laboratories

Date of Approval of NDA Insert and Supplement #: S-016, 7/15/98

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: Side-by-side

Basis of Approval for the Carton Labeling: NA

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		x	
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?			x
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		x	
Does the package proposed have any safety and/or regulatory concerns?		x	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		x	
Is the strength and/or concentration of the product unsupported by the insert labeling?		x	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		x	
Are there any other safety concerns?		x	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths?			x
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		x	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		x	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		x	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			x
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			

Is the scoring configuration different than the RLD?		x	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?	x		
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		x	
Do any of the inactives differ in concentration for this route of administration?		x	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		x	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		x	
Has the term "other ingredients" been used to protect a trade secret?* If so, is claim supported?** [SEE FTR]		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			x
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		x	
Does USP have labeling recommendations? If any, does ANDA meet them?			x
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		x	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			x
Bioequivalence Issues: (Compare bioeqivalency values: insert to study. List Cmax, Tmax, T ½ and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	x		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		x	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD: (portions taken from previous review)

1. MODEL LABELING - Ticlid®; Syntex Laboratories, Inc.;
   Approved Julv 15, 1998;
   This is NDA /SLR-015.

2. This drug product is not the subject of a USP monograph.

3. The listing of inactive ingredients in the DESCRIPTION section of the package insert appear to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 127, vol.B.1.1.

4. We will not ask to reduce the prominence of the "CLINICAL TRIALS" section heading, which is consistent with the innovator's.

5. PATENTS/EXCLUSIVITIES - Per the Orange Book, 19th Edition through Supp 1, the patent 4591592 expires on 5/27/2003 without any listed exclusivity. The firm's statement is accurate. However, the firm has filed Paragraph IV Patent Certification.

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

   NDA: Store at 15° to 30°C (59° to 86°F).

   ANDA: Store at controlled room temperature 15° to 30°C (59° to 86°F).

7. DISPENSING STATEMENT

   RLD - IMPORTANT: Dispense enclosed Patient Package Insert with prescription.

   ANDA - Dispense contents with a child-resistant closure as required, and in a tight, light-resistant container as defined in the USP. **Important:** Dispense enclosed Patient Package Insert with prescription.

8. PACKAGING CONFIGURATIONS

   RLD: 30s, 60s, 500s, and unit-dose 100s.
   ANDA: 30s, 60's, & 500s

9. The tablets have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. See Vol.B.1.3, p.0616.

10. SCORING - The RLD is not scored. The ANDA is not scored.

11. CONTAINER/CLOSURE

    Container: HDPE

    30's, 60's - CRC
    500's - Non-CRC [p.565, vol.B.1.3]

12. A meeting with new drugs on February 18, 1999, resulted in an agreement to request that all generic ticlopidine applicants provide an educational program that will include essential elements that will be identified by the new drugs division. This meeting was in response to Dr. Janet

Woodcock's statement that the generic firms should do what Roche did to help prevent life-threatening hematological adverse reactions. A letter was issued on June 15, 1999 requesting sponsors to submit their post-approval plan for their educational program. On June 22, 1999, Eon submitted their plan which included a 'Dear Doctor' letter, advertisement of educational material in the JAMA and other health related journals, and the dispensing of PPI. This plan was forwarded to Gary Buehler and then to Dr. Mary Fanning for approval (acceptability).

Date of Review: 6-10-99 **Date of Submission:** 4-27-99

Primary Reviewer: Adolph Vezza **Date:** 7/9/99

A. Vezza

Team Leader: Charlie Hoppes **Date:** /S/ 7/12/99

C.L. for

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cc: Comm. /S/ 7/12/1999

DIVISION APPROVAL SUMMARY

ANDA: 75-326 **DRUG PRODUCT:** Ticlopidine hydrochloride, Tablets

FIRM: Eon Labs Manufacturing, Inc.

DOSAGE: Tablet **STRENGTH:** 250 mg

CGMP STATEMENT/EIR UPDATE STATUS:
CGMP: Statement provided on page 262 (vol 1.1).
EIR: Acceptable dated 5/28/99.

BIO STUDIES/BIOEQUIVALENCE STATUS:
Bio waiver granted on 10/28/98.

METHODS VALIDATION:
Field had conducted methods verification and found them suitable. Results filed in volume 4.1.

STABILITY (conditions, containers and methods):
Bio batch was setup on stability in the proposed container/closure systems and data are reported. The bio batch was packaged in 30, 60, and 500 count bottles. The following are the firm's tests and specifications.

Test	Specification
Description	White to off-white, oval, film coated tablets with imprints 'E115' on one side
Dissolution - 900 mL - U.S.P. APPARATUS 2 (PADDLE): 50 RPM (water medium)	es
RELATED COMPOUNDS	
Individual known impurities	
Individual unknown imp.	
Total impurities	
Assay (U.S.P.) -	

LABELING REVIEW STATUS:
Acceptable dated 6/10/99.

STERILIZATION VALIDATION (If Applicable):
NA

BATCH SIZES:
Bio batch (identity #, drug substance source):
The drug substance supplier is
Lot # 6667A is used for the manufacture of batch. The bio batch size is tablets.

STABILITY BATCH (different from bio batch, manu. Site, process):
Stability batch is the same as bio batch.

PROPOSED PRODUCTION BATCH:
Tablets is proposed for commercial scale. Reprocessing statement is enclosed on page 317.

COMMENTS:
None.

CHEMISTRY REVIEWER: Radhika Rajagopalan, Ph.D.
DATE: 7/21/99

8/6/99

8/16/99