CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75161

CHEMISTRY REVIEW(S)

1. CHEMIST'S REVIEW NO. 3

2. ANDA # 75-161

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

4. LEGAL BASIS FOR ANDA SUBMISSION
Patent no. 4591592 which covers the RLD will expire on May 27, 2003.

5. PROPRIETARY NAME
NA

6. NONPROPRIETARY NAME
Ticlopidine Hydrochloride

9. AMENDMENTS AND OTHER DATES
July 8, 1997-- Original Submission
August 15, 1997-- Acknowledgment receipt
November 6, 1997-- Deficiency letter
April 3, 1998-- Amendment
April 30, 1998-- New correspondence
May 6, 1998-- New correspondence
August 11, 1998-- Deficiency letter (labeling)
September 21, 1998--Labeling letter
September 9, 1998-- Deficiency letter (chem)
September 22, 1998--Amendment
October 1, 1998-- Correspondence
November 11, 1998—Amendment
June 15, 1 999- TA granted
July 28, 1999- New correspondence
August 13, 1999- Amendment (label)
August 18, 1999- Minor amendment

10. PHARMACOLOGICAL CATEGORY
Platelet aggregation inhibitor (reduces risk of thrombotic stroke)

11. Rx or OTC
Rx

12. RELATED DMFs Nos.

13. DOSAGE FORM
Tablets

14. POTENCY
250 mg

15. CHEMICAL NAME AND STRUCTURE
5-[(2-chloro-phenyl)methyl]-4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride

16. RECORDS AND REPORTS
N/A

17. COMMENT
The firm filed a minor amendment to convert the TA to a full approval as required with all the changes that have been made. The following are noted: Excipient's specifications are updated as per compendia. The drug product's specifications for Europe are provided (updated). Methods for the drug product are updated and sample examination is added. Specifications are updated for the packaging components. The DMF had been amended by the holder. The amendment was reviewed on 9/3/99 and found adequate.

18. CONCLUSION AND RECOMMENDATIONS
Recommend approval letter to issue.

19. REVIEWER:
Radhika Rajagopalan, Ph.D.

DATE COMPLETED:
September 3, 1999

SEP 9 1998

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-161 APPLICANT: Genpharm

DRUG PRODUCT: Ticlopidine Tablets USP, 250 mg

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies

1. We acknowledge receiving the revised total coated tablet weight gain limit from % (ANDA batch) to % (Scale-up). The original proposal required that the scale-up batches not surpass % of the total coated tablet weight gain. Again, please justify the difference in total tablet coated weight gain limit as the demonstration batch was % and the proposed limit for scale-up batches could go as low as % or as high as %. Could this difference adversely impact the dissolution of the finished dosage form?

2. We acknowledge receiving the revised known/unknown impurities release and stability specifications from NMT % individual & NMT % total to NMT % individual known/unknown & NMT % total. The release and stability data obtained for the demonstration batch reflect that the single largest unknown impurities specification could be revised to NMT %. Please revise and resubmit the single largest unknown release and stability specification to NMT %.

   Also, the comparative impurity profile vs. the RLD submitted is found difficult to evaluate. The representative chromatograms for the subject study should be more specific since we are not sure if all the unknown products are being quantitated appropriately. Please include a placebo sample chromatogram.

3. Regarding the method for the related substances: 1) please include your rationale for removing the known impurities from the standard preparation; 2) justify the omission of a purity correction factor for ticlopidine HCl reference standard in the final calculations; and 3) specify whether the peak area or the peak height is to be used in the final calculation (we recommend the peak area be the preferred mechanism for the subject calculation).

4. It is noted that the assay test results reported for each of the prescribed room temperature stability test intervals shows a gradual increase in the assay values (e.g., %). Could you provide a reasonable explanation for such an unusual behavior?

B. In addition to responding to the deficiencies presented below, please note and acknowledge the following comment in your response:

DMF was reviewed and found to be deficient. These were directly conveyed to the holder and should be answered satisfactorily before the application can be approved.

Sincerely yours,

/S/

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

NOV 6 1997

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-161 APPLICANT: Genpharm, Inc.

DRUG PRODUCT: Ticlopidine HCl Tablets, 250 mg

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies

1. Please revise your component and composition statement to reflect the amount of ticlopidine hydrochloride that is equivalent to the base.

2. Please provide a letter from your drug substance manufacturer indicating compliance with USP OVI specifications.

3. A regulatory limit for the "sum of unknown impurities" for drug substance release purposes should be established. Please revise and resubmit.

4. The coating solution's projected percentages of "Total Solids" and a viscosity regulatory range should be provided. Also, please justify the difference in total tablet coated weight gain as the demonstration batch was % and scale-up batches will be %. Could this difference adversely impact the dissolution of the finished dosage form?

5. The proposed known/unknown impurities release and stability specifications are considered to be too broad. Please revise according to the data obtained for the demonstration batch. Also, a regulatory range for the "sum of unknown impurities" should be established.

   Furthermore, please justify the individual and total unknown impurities specifications. A comparative impurity profile vs. the RLD should be submitted and include representative chromatograms for the subject study.

6. Thickness and hardness regulatory ranges should be established, based on the data acquired for the demonstration batch, before the application can be approved. Please provide.

7. DMF is presently under review. If deficiencies are found, these will be directly conveyed to the holder and should be answered satisfactorily before the application can be approved. Please acknowledge.

B. In addition to responding to the deficiencies presented below, please note and acknowledge the following comment in your response:

Since your drug substance and drug product are non-compendial items, we have requested the Philadelphia District Laboratory to conduct a methods validation. The application will not be approved until the method validation has been found to be acceptable.

Sincerely yours,

/S/

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research