CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 12-649/S046

APPROVAL LETTER

NDA 12-649/S-046

SEP 2 4 1999

Merck and Co., Inc.
Sunmeytown Pike
P.O. Box 4
West Point, PA 19486

Attention: Dennis M. Erb, Ph.D.
Senior Director, Regulatory Affairs

Dear Dr. Erb:

Please refer to your supplemental new drug application dated August 13, 1999, received August 16, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Periactin (cyproheptadine HCl) Tablets, 4 mg.

We note that this supplement was submitted as 'Special Supplement, Changes Being Effected' under 21 CFR 3 14.70(c).

This supplemental new drug application provides for deletion of information about Periactin Syrup, and revisions to the package insert accordingly. Your submission stated January 1, 2000, as the implementation date for these changes.

We have completed the review of this supplemental application, and have the editorial revisions listed below. Accordingly, this supplemental application is approved effective on the date of this letter.

Since the syrup formulation is no longer available, the following changes should be addressed in the Pharmacokinetics and Metabolism subsection of CLINICAL PHARMACOLOGY.

1. Remove "or syrup" from the sentence "After a single 4 mg oral dose of ^{14}C-labelled cyproheptadine HCl in normal subjects, given as tablets or syrup."

2. Remove the sentence "No significant difference in the mean urinary excretion exists between the tablet and syrup formulations."

3. Remove "of PERIACTIN Syrup" from the sentence "No detectable amounts of unchanged drug were present in the urine of patients on chronic 12-20 mg daily doses of PERIACTIN Syrup."

The final printed labeling (FPL) must be identical with the changes indicated, to the submitted draft labeling (package insert submitted August 13, 1999). These revisions are terms of the NDA supplement approval.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed to each application. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 12-649/S-046. Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Ms. Ladan Jafari, Project Manager, at (301) 827-5584.

Sincerely,

Robert J. Meyer, M.D.
Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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FINAL PRINTED LABELING

FINAL PRINTED LABELING HAS NOT BEEN SUBMITTED TO THE FDA

DRAFT LABELING IS **NO LONGER** BEING SUPPLIED SO AS TO ENSURE ONLY CORRECT AND CURRENT INFORMATION IS DISSEMINATED TO THE PUBLIC.

NDA 13-220/S-042
NDA 12-649/S-046

SEP 20 1999

PROJECT MANAGER LABELING REVIEW

DATE: 9-1-99

DRUG: Periactin Syrup & Tablets

BACKGROUND: Merck and Co., Inc. submitted supplemental new drug applications to NDA 13-220/S-042 and NDA 12-649/S-046 dated August 13, 1999. These supplements provide for deletion of information about Periactin Syrup, since the syrup formulation was discontinued from domestic production and is no longer marketed. Supplement 12-649/S-046 also provides for revisions to the following sections of the package insert.

1. DESCRIPTION: Deletion of information about Pericatin Syrup.
   Conclusion: Acceptable

2. WARNING: Addition of "see PRECAUTIONS, Geriatric Use."
   Conclusion: Acceptable

3. PRECAUTIONS: Addition of Geriatric Use subsection. Provides general statement regarding use in geriatric population. No specific information is available for Periactin. Conclusion: Acceptable

4. ADVERSE REACTIONS: Addition of the following adverse events: cholestasis, hepatic failure, hepatitis, and hepatic function abnormality.
   Conclusion: Acceptable

5. DOSAGE AND ADMINISTRAION: Deletion of the reference to [redacted]
   : Deletion of information about Periactin Syrup.
   : Retention of mg/kg/day dose.
   Conclusion: Acceptable for estimating appropriate dose of tablet.

6. HOW SUPPLIED: Deletion of information about Periactin Syrup.
   Conclusion: Acceptable

7. "Children" now reads "pediatric patients" throughout the package insert.
   Conclusion: Acceptable

COMMENTS: Although the new package insert is for the tablet formulation only, there are still references to the syrup formulation in the Pharmacokinetics and Metabolism subsection of CLINICAL PHARMACOLOGY. Sponsor should be advised to remove these references.

Elimination of the syrup formulation, raised concern that the tablet formulation may not address the pediatric dosage form for children ages 2-6. Review of Merck's latest approved supplement (SLR-045) revealed that dosage form for this patient population has already been approved.

Recommendations: Approval is recommended for these supplements. Need to inform the sponsor to correct references to Syrup formulation.

Project Manager /S/

Concurrence by all disciplines:

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 12-649/S046

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

DIO file

SEP 21 1999

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 12,649 (S046)	**REVIEWER:** Young-Moon Choi, Ph.D.
DRUG: Periactin (cyproheptadine HCl) tablet	**SUBMISSION :** 8/13/99
SPONSOR: Merk and Co., Inc.	**STAMPED :** 8/16/99 for both submissions
TYPE OF SUBMISSION: Special supplement, Changes Being Effected (Labeling change)	**REVIEWED:** 9/21/99

Synopsis
The sponsor will remove the Periactin Syrup formulation from the market. Accordingly, the current labeling for both syrup and tablet should be changed as appropriate.

Comment
The following changes should be addressed in the Pharmacokinetics and Metabolism subsection of CLINICAL PHARMACOLOGY.

1. Remove "or syrup" from the sentence "After a single 4mg oral dose of ^{14}C-labelled cyproheptadine HCl in normal subjects, given as tablets or syrup."
2. Remove the sentence "No significant difference in the mean urinary excretion exists between the tablets and syrup formulations."
3. Remove "of PERIACTIN Syrup" from the sentence "No detectable amounts of unchanged drug were present in the urine of patients on chronic 12-20 mg daily doses of PERIACTIN Syrup.

Recommendation
The Office of Clinical Pharmacology and Biopharmaceutics reviewed the proposed labeling change. The above labeling comment needs to be sent to the sponsor. This comment already has been communicated to the Project Manager.

/S/ 9/21/99

APPEARS THIS WAY
ON ORIGINAL

Young Moon Choi, Ph.D.
Pharmacokineticist
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics