CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 17-533/S-031

Name:	Klonopin Tablets
Generic Name:	clonazepam
Sponsor:	Hoffmann-La Roche, Inc.
Approval Date:	04/11/01

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APPLICATION NUMBER:

NDA 17-533/S-031

CONTENTS

Reviews / Information Included in this Review	
Approval Letter	X
Approvable Letter(s)	
Final Printed Labeling	
Medical Review(s)	X
Chemistry Review(s)	
EA/FONSI	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	
Administrative and Correspondence Document(s)	X

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APPLICATION NUMBER:

NDA 17-533/S-031

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 17-533/S-031

Hoffmann-La Roche Inc.
Attention: Duane Voss
Program Director, Drug Regulatory Affairs
340 Kingsland Street
Nutley, NJ 07110

Dear Mr. Voss:

Please refer to your supplemental new drug application dated August 26, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Klonopin (clonazepam) 0.5 mg, 1 mg, and 2 mg Tablets.

This supplemental application provides for the creation of a new subsection under the **PRECAUTIONS** section entitled **Geriatric Use** to comply with an August 27, 1997 Federal Register Notice requiring that sponsors add geriatric use data to product labeling.

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, this supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted August 26, 1998).

Please submit the copies of final printed labeling (FPL) electronically to the application according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. 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 17-533/S-031." 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, call Mr. Paul David, R.Ph., Senior Regulatory Project Manager, at (301) 594-5530.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

/s/

Russell Katz
4/11/01 08:48:42 AM

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APPLICATION NUMBER:

NDA 17-533/S-031

MEDICAL REVIEW(S)

REVIEW AND EVALUATION OF LABELING SUPPLEMENT

NDA:	**Special Supplement-Changes Being Effected Amendment to NDA 17-533 Supplement 031**
DRUG:	**Klonopin (clonazepam) Tablets Labeling Supplement-Geriatric Use**
STRENGTHS	**0.5mg, 1 mg, 2 mg**
SUBMISSION DATE:	**August, 28, 1998**
REVIEW DATE:	**April 22, 1999**

In a Federal Register notice date August 27, 1997, FDA published a final rule which established, in new Section 201.57(f)(10), a "Geriatric Use" subsection of prescription drug labeling that provides information on the safe and effective use of drugs in patients aged 65 and older. Subsequently, the firm is submitting a supplemental application for priority implemental to comply with the new requirement. Klonopin is indicated as monotherapy or adjunct in the treatment of Lennox-Gastaut syndrome, akinetic and myoclonic seizures. Klonopin is also indicated for the treatment of panic disorder with or without agoraphobia.

The firm conducted a literature search covering the life of the product through April 6, 1998 which discovered a few studies with very small geriatric populations. However, not only were these studies too small upon which to base usage recommendations, they were all for non-labeled indications (dementia, essential tremor, Parkinsonian dysarthria). No apparent safety issues in geriatric patients were identified in these small trials. Also, the firm (Roche) reviewed their safety information, which did not locate any events which appeared to occur with greater frequency in geriatric patients compared with all patients.

The current package insert contains no geriatric information. To comply with the final rule. Roche has revised the package insert to add a "Geriatric Use" subsection under the PRECAUTIONS section. Within this section, statements regarding the use of sedative drugs and renally excreted drugs in the elderly have been added. Statements based on text in the "Geriatric Use" subsection have been added to the DOSAGE AND ADMINISTRATION section under both "Seizure Disorder" and "Panic Disorder".

> Geriatric Use: Clinical studies of Klonopin did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from youger subjects . Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious,

usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

Because clonazepam undergoes hepatic metabolism, it is possible that liver disease will impair clonazepam elimination. Metabolites of Klonopin are excreted by the kidneys; to avoid their excess accumulation, caution should be exercised in the administration of the drug to patients with impaired renal function. Because elderly patients are more likely to have decreased hepatic and/or renal function, care should be taken in dose selection, and it may be useful to assess hepatic and/or renal function at the time of dose selection.

Sedating drugs may cause confusion and over-sedation in the elderly; elderly patients generally should be started on low doses of Klonopin and observed closely.

COMMENT AND RECOMMENDATION

This labeling supplement is adequate and should be approved.

Janeth Rouzer-Kammeyer, MD.

Cc NDA17-533/SLR-031
CcHFD-120/RKatz/JRouzer-Kammeyer/JWare
5-7-99

/s/

Janeth Rouzer
3/20/01 02:05:11 PM
MEDICAL OFFICER

John Feeney
4/11/01 10:57:39 AM
MEDICAL OFFICER

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APPLICATION NUMBER:

NDA 17-533/S-031

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

REGULATORY PROJECT MANAGER
LABELING REVIEW

Review Date: March 16, 2001
NDA: 17-533
Sponsor: Hoffmann-La Roche
DRUG: Klonopin (clonazepam) 0.5 mg, 1 mg, and 2 mg Tablets

Supplements: SLR-031 dated 8-26-98

Notes of interest:

- The last approved labeling was SE1-023 (approval of Panic Disorder) which was approved in an Agency letter dated 4-9-97, and FPL was submitted on 7-3-97

REVIEW

17-533/SLR-031
Dated: 8-26-98
CBE: No
Label Code:N/A, Draft Labeling
Reviewed by Medical Officer: Yes, acceptable.

This supplemental application provides for the creation of a new subsection under the **PRECAUTIONS** section entitled **Geriatric Use** to comply with an August 27, 1997 Federal Register Notice requiring that sponsors add geriatric use data to product labeling.

CONCLUSIONS

1. This supplement only provides for the labeling revisions listed above.
2. The medical officer concurs with the revisions provided for in the application
3. I recommend that a letter issue for SLR-031 approving the supplement and requesting 20 copies of FPL.

Paul David. RPh
Regulatory Project Manager

John Purvis
Supervisory Consumer Safety Officer

/s/

Paul David
3/20/01 01:49:39 PM
CSO

Robbin Nighswander
3/21/01 03:04:31 PM
CSO
Signed for Jack Purvis, SCSO.