CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75150

APPROVAL LETTER

ANDA 75-150

OCT 5 1998

Mylan Pharmaceuticals, Inc.
Attention: Frank R. Sisto
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Sir:

This is in reference to your abbreviated new drug application dated June 27, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Clonazepam Tablets USP, 0.5 mg, 1 mg and 2 mg.

Reference is also made to your amendments dated August 12, and September 3, 1997; and March 19, March 26, and August 24, 1998.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Clonazepam Tablets USP, 0.5 mg, 1 mg and 2 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Klonopin Tablets, 0.5 mg, 1 mg and 2 mg, respectively, of Hoffmann La Roche, Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final

printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/ for 10/5/98

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75150

DRAFT FINAL PRINTED LABELING

Interference With Cognitive and Motor Performance: Be- ... have the

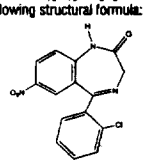
CZPM:R3

OCT 5 1988

CLONAZEPAM TABLETS, USP

0.5 mg, 1 mg and 2 mg

DESCRIPTION: Clonazepam is a benzodiazepine and chemically designated as clonazepam is 5-(*o*-Chlorophenyl)-1,3-dihydro-7-nitro-2*H*-1,4-benzodiazepin-2-one. It is a light yellow crystalline powder. It has a molecular weight of 315.72, molecular formula of $C_{15}H_{10}ClN_3O_3$ and the following structural formula:



Each tablet, for oral administration contains 0.5 mg, 1 mg, or 2 mg of clonazepam. In addition, each tablet contains the following inactive ingredients: anhydrous lactose, colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, pregelatinized starch, and sodium lauryl sulfate. Additionally, the 0.5 mg tablets contain D&C yellow #10. The 1 mg tablets contain D&C yellow #10 and FD&C blue #1 lake.

CLINICAL PHARMACOLOGY:

Pharmacodynamics: The precise mechanism by which clonazepam exerts its antiseizure effects is unknown, although it is believed to be related to its ability to enhance the activity of gamma aminobutyric acid (GABA), the major inhibitory neurotransmitter in the central nervous system. Convulsions produced in rodents by pentylenetetrazol or, to a lesser extent, electrical stimulation are antagonized, as are convulsions produced by photic stimulation in susceptible baboons. A taming effect in aggressive primates, muscle weakness and hypnosis are also produced. In humans, clonazepam is capable of suppressing the spike and wave discharge in absence seizures (petit mal) and decreasing the frequency, amplitude, duration and spread of discharge in minor motor seizures.

Pharmacokinetics: Clonazepam is rapidly and completely absorbed after oral administration. The absolute bioavailability of clonazepam is about 90%. Maximum plasma concentrations of clonazepam are reached within 1 to 4 hours after oral administration. Clonazepam is approximately 85% bound to plasma proteins. Clonazepam is highly metabolized, with less than 2% unchanged clonazepam being excreted in the urine. Biotransformation occurs mainly by reduction of the 7-nitro group to the 4-amino derivative. This derivative can be acetylated, hydroxylated, and glucuronidated. Cytochrome P-450, including CYP3A, may play an important role in clonazepam reduction and oxidation. The elimination half-life of clonazepam is typically 30 to 40 hours. Clonazepam pharmacokinetics are dose-independent throughout the dosing range. There is no evidence that clonazepam induces its own metabolism or that of other drugs in humans.

Pharmacokinetics in Demographic Subpopulations and in Disease States: Controlled studies examining the influence of gender and age on clonazepam pharmacokinetics have not been conducted, nor have the effects of renal or liver disease on clonazepam pharmacokinetics been studied. Because clonazepam undergoes hepatic metabolism, it is possible that liver disease will impair clonazepam elimination. Thus, caution should be exercised when administering clonazepam to these patients.

INDICATIONS AND USAGE: Seizure Disorders: Clonazepam is useful alone or as an adjunct in the treatment of the Lennox-Gastaut syndrome (petit mal variant), akinetic and myoclonic seizures. In patients with absence seizures (petit mal) who have failed to respond to succinimides, clonazepam may be useful.

In some studies, up to 30% of patients have shown a loss of anticonvulsant activity, often within 3 months of administration. In some cases, dosage adjustment may reestablish efficacy.

CONTRAINDICATIONS: Clonazepam should not be used in patients with a history of sensitivity to benzodiazepines, nor in patients with clinical or biochemical evidence of significant liver disease. It may be used in patients with open angle glaucoma who are receiving appropriate therapy, but is contraindicated in acute narrow angle glaucoma.

WARNINGS: Interference with Cognitive and Motor Performance: Since clonazepam produces CNS depression, patients receiving this drug should be cautioned against engaging in hazardous occupations requiring mental alertness, such as operating machinery or driving a motor vehicle. They should also be warned about the concomitant use of alcohol or other CNS-depressant drugs during clonazepam therapy (see Drug Interactions and Information for Patients under PRECAUTIONS).

Pregnancy Risks: Data from several sources raise concerns about the use of clonazepam during pregnancy.

Animal Findings: In three studies in which clonazepam was administered orally to pregnant rabbits at doses of 0.2, 1, 5, or 10 mg/kg/day (low dose approximately 0.2 times the maximum recommended daily human dose of 20 mg/day on a mg/m^2 basis) during the period of organogenesis, a similar pattern of malformations (cleft palate, open eyelid, fused sternebrae and limb defects) was observed in a low, non-dose-related incidence in exposed litters from all dosage groups. Reductions in maternal weight gain occurred at dosages of 5 mg/kg/day or greater and reduction in embryo-fetal growth occurred in one study at a dosage of 10 mg/kg/day. No adverse maternal or embryo-fetal effects were observed in mice and rats following administration during organogenesis of oral doses up to 15 mg/kg/day or 40 mg/kg/day, respectively (4 and 20 times the maximum recommended human dose of 20 mg/day on a mg/m^2 basis).

General Concerns and Considerations About Anticonvulsants: Recent reports suggest an association between the use of anticonvulsant drugs by women with epilepsy and an elevated incidence of birth defects in children born to these women. Data are more extensive with respect to diphenylhydantoin and phenobarbital, but these are also the most commonly prescribed anticonvulsants; less systematic or anecdotal reports suggest a possible similar association with the use of all known anticonvulsant drugs.

In children of women treated with drugs for epilepsy, reports suggesting an elevated incidence of birth defects cannot be regarded as adequate to prove a definite cause and effect relationship. There are intrinsic methodologic problems in obtaining adequate data on drug teratogenicity in humans; the possibility also exists that other factors, e.g., genetic factors or the epileptic condition itself, may be more important than drug therapy in leading to birth defects. The great majority of mothers on anticonvulsant medication deliver normal infants. It is important to note that anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy; however, it cannot be said with any confidence that even mild seizures do not pose some hazards to the developing embryo or fetus.

General Concerns About Benzodiazepines: An increased risk of congenital malformations associated with the use of benzodiazepine drugs has been suggested in several studies.

There may also be non-teratogenic risks associated with the use of benzodiazepines during pregnancy. There have been reports of neonatal flaccidity, respiratory and feeding difficulties, and hypothermia in children born to mothers who have been receiving benzodiazepines late in pregnancy. In addition, children born to mothers receiving benzodiazepines late in pregnancy may be at some risk of experiencing withdrawal symptoms during the postnatal period.

Advice Regarding the Use of Clonazepam in Women of Childbearing Potential: In general, the use of clonazepam in women of childbearing potential, and more specifically during known pregnancy, should be considered only when the clinical situation warrants the risk to the fetus.

The specific considerations

The specific considerations addressed above regarding the use of anticonvulsants for epilepsy in women of childbearing potential should be weighed in treating or counseling these women.

Because of experience with other members of the benzodiazepine class, clonazepam is assumed to be capable of causing an increased risk of congenital abnormalities when administered to a pregnant woman during the first trimester. The possibility that a woman of childbearing potential may be pregnant at the time of institution of therapy should be considered. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Patients should also be advised that if they become pregnant during therapy or intend to become pregnant they should communicate with their physician about the desirability of discontinuing the drug.

Withdrawal Symptoms: Withdrawal symptoms of the barbiturate type have occurred after the discontinuation of benzodiazepines (see DRUG ABUSE AND DEPENDENCE section).

PRECAUTIONS: General: ***Worsening of Seizures:*** When used in patients in whom several different types of seizure disorders coexist, clonazepam may increase the incidence or precipitate the onset of generalized tonic-clonic seizures (grand mal). This may require the addition of appropriate anticonvulsants or an increase in their dosages. The concomitant use of valproic acid and clonazepam may produce absence status.

Laboratory Testing During Long-Term Therapy: Periodic blood counts and liver function tests are advisable during long-term therapy with clonazepam.

Risks of Abrupt Withdrawal: The abrupt withdrawal of clonazepam, particularly in those patients on long-term, high-dose therapy, may precipitate status epilepticus. Therefore, when discontinuing clonazepam, gradual withdrawal is essential. While clonazepam is being gradually withdrawn, the simultaneous substitution of another anticonvulsant may be indicated.

Caution in Renally Impaired Patients: Metabolites of clonazepam 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.

Hypersalivation: Clonazepam may produce an increase in salivation. This should be considered before giving the drug to patients who have difficulty handling secretions. Because of this and the possibility of respiratory depression, clonazepam should be used with caution in patients with chronic respiratory diseases.

Information for Patients: Physicians are advised to discuss the following issues with patients for whom they prescribe clonazepam.

Dose Changes: To assure the safe and effective use of benzodiazepines, patients should be informed that, since benzodiazepines may produce psychological and physical dependence, it is advisable that they consult with their physician before either increasing the dose or abruptly discontinuing this drug.

Interference With Cognitive and Motor Performance: Because benzodiazepines have the potential to impair judgment, thinking or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles until they are reasonably certain that clonazepam therapy does not affect them adversely.

Pregnancy: Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy with clonazepam (see WARNINGS).

Nursing: Patients should be advised not to breast-feed an infant if they are taking clonazepam.

Concomitant Medication: Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions.

Alcohol: Patients should be advised to avoid alcohol while taking clonazepam.

Drug Interactions: ***Effect of Clonazepam on the Pharmacokinetics of Other Drugs:*** Clonazepam does not appear to alter the pharmacokinetics of phenytoin, carbamazepine, or phenobarbital. The effect of clonazepam on the metabolism of other drugs has not been investigated.

Effect of Other Drugs on the Pharmacokinetics of Clonazepam: Ranitidine and propantheline, agents that decrease stomach acidity, do not greatly alter clonazepam pharmacokinetics. Fluoxetine does not affect the pharmacokinetics of clonazepam. Cytochrome P-450 inducers, such as phenytoin, carbamazepine, and phenobarbital induce clonazepam metabolism, causing an approximately 30% decrease in plasma clonazepam levels. Although clinical studies have not been performed, based on the involvement of the cytochrome P-450 3A family in clonazepam metabolism, inhibitors of this enzyme system, notably oral antifungal agents, should be used cautiously in patients receiving clonazepam.

Pharmacodynamic Interactions: The CNS-depressant action of the benzodiazepine class of drugs may be potentiated by alcohol, narcotics, barbiturates, nonbarbiturate hypnotics, antianxiety agents, the phenothiazines, thioxanthene and butyrophenone classes of antipsychotic agents, monoamine oxidase inhibitors and the tricyclic antidepressants, and by other anticonvulsant drugs.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenicity studies have not been conducted with clonazepam.

The data currently available are not sufficient to determine the genotoxic potential of clonazepam.

In a two generation fertility study in which clonazepam was given orally to rats at 10 and 100 mg/kg/day (low dose approximately 5 times the maximum clinical dose of 20 mg/day on a mg/m^2 basis), there was a decrease in the number of pregnancies and in the number of offspring surviving until weaning.

Pregnancy: ***Teratogenic Effects - Pregnancy Category D:*** See WARNINGS.

Labor and Delivery: The effect of clonazepam on labor and delivery in humans has not been specifically studied, however, perinatal complications have

ing until weaning.

Pregnancy: *Teratogenic Effects - Pregnancy Category D:* See WARNINGS.

Labor and Delivery: The effect of clonazepam on labor and delivery in humans has not been specifically studied, however, perinatal complications have been reported in children born to mothers who have been receiving benzodiazepines late in pregnancy, including findings suggestive of either excess benzodiazepine exposure or of withdrawal phenomena (see Pregnancy Risks under WARNINGS).

Nursing Mothers: Mothers receiving clonazepam should not breast-feed their infants.

Pediatric Use: Because of the possibility that adverse effects on physical or mental development could become apparent only after many years, a benefit-risk consideration of the long-term use of clonazepam is important in patients (see INDICATIONS and DOSAGE AND ADMINISTRATION sections).

ADVERSE REACTIONS: The most frequently occurring side effects of clonazepam are referable to CNS depression. Experience has shown that drowsiness has occurred in approximately 50% of patients and ataxia in approximately 30%. In some cases, these may diminish with time; behavior problems have been noted in approximately 25% of patients. Others, listed by system, are:

Neurologic: Abnormal eye movements, aphonia, choreiform movements, coma, diplopia, dysarthria, dysdiadochokinesis, "glassy-eyed" appearance, headache, hemiparesis, hypotonia, nystagmus, respiratory depression, slurred speech, tremor, vertigo.

Psychiatric: Confusion, depression, amnesia, hallucinations, hysteria, increased libido, insomnia, psychosis, suicidal attempt (the behavior effects are more likely to occur in patients with a history of psychiatric disturbances). The following paradoxical reactions have been observed: excitability, irritability, aggressive behavior, agitation, nervousness, hostility, anxiety, sleep disturbances, nightmares and vivid dreams.

Respiratory: Chest congestion, rhinorrhea, shortness of breath, hypersecretion in upper respiratory passages.

Cardiovascular: Palpitations.

Dermatologic: Hair loss, hirsutism, skin rash, ankle and facial edema.

Gastrointestinal: Anorexia, coated tongue, constipation, diarrhea, dry mouth, encopresis, gastritis, increased appetite, nausea, sore gums.

Genitourinary: Dysuria, enuresis, nocturia, urinary retention.

Musculoskeletal: Muscle weakness, pains.

Miscellaneous: Dehydration, general deterioration, fever, lymphadenopathy, weight loss or gain.

Hematopoietic: Anemia, leukopenia, thrombocytopenia, eosinophilia.

Hepatic: Hepatomegaly, transient elevations of serum transaminases and alkaline phosphatase.

DRUG ABUSE AND DEPENDENCE: Controlled Substance Class: Clonazepam is a Schedule IV controlled substance.

Physical and Psychological Dependence: Withdrawal symptoms, similar in character to those noted with barbiturates and alcohol (e.g., convulsions, psychosis, hallucinations, behavioral disorder, tremor, abdominal and muscle cramps) have occurred following abrupt discontinuance of clonazepam. The more severe withdrawal symptoms have usually been limited to those patients who received excessive doses over an extended period of time. Generally milder withdrawal symptoms (e.g. dysphoria and insomnia) have been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months. Consequently, after extended therapy, abrupt discontinuation should generally be avoided and a gradual dosage tapering schedule followed (see DOSAGE AND ADMINISTRATION section). Addiction-prone individuals (such as drug addicts or alcoholics) should be under careful surveillance when receiving clonazepam or other psychotropic agents because of the predisposition of such patients to habituation and dependence.

OVERDOSAGE: Human Experience: Symptoms of clonazepam overdosage, like those produced by other CNS depressants, include somnolence, confusion, coma and diminished reflexes.

Overdose Management: Treatment includes monitoring of respiration, pulse and blood pressure, general supportive measures and immediate gastric lavage. Intravenous fluids should be administered and an adequate airway maintained. Hypotension may be combated by the use of levarterenol or metaraminol. Dialysis is of no known value.

Flumazenil, a specific benzodiazepine-receptor antagonist, is indicated for the complete or partial reversal of the sedative effects of benzodiazepines and may be used in situations when an overdose with a benzodiazepine is known or suspected. Prior to the administration of flumazenil, necessary measures should be instituted to secure airway, ventilation and intravenous access. Flumazenil is intended as an adjunct to, not as a substitute for, proper management of benzodiazepine overdose. Patients treated with flumazenil should be monitored for resedation, respiratory depression and other residual benzodiazepine effects for an appropriate period after treatment. **The prescriber should be aware of a risk of seizure in association with flumazenil treatment, particularly in long-term benzodiazepine users and in cyclic antidepressant overdose.** The complete flumazenil package insert, including CONTRAINDICATIONS, WARNINGS and PRECAUTIONS, should be consulted prior to use.

Flumazenil is not indicated in patients with epilepsy who have been treated with benzodiazepines. Antagonism of the benzodiazepine effect in such patients may provoke seizures.

Serious sequelae are rare unless other drugs or alcohol have been taken concomitantly.

DOSAGE AND ADMINISTRATION: Adults: The initial dose for adults should not exceed 1.5 mg/day divided into three doses. Dosage may be increased in increments of 0.5 to 1 mg every 3 days until seizures are adequately controlled or until side effects preclude any further increase. Maintenance dosage must be individualized for each patient depending upon response. Maximum recommended daily dose is 20 mg.

The use of multiple anticonvulsants may result in an increase of depressant adverse effects. This should be considered before adding clonazepam to an existing anticonvulsant regimen.

Pediatric Patients: Clonazepam is administered orally. In order to minimize drowsiness, the initial dose for infants and children (up to 10 years of age or 30 kg of body weight) should be between 0.01 and 0.03 mg/kg/day but not to exceed 0.05 mg/kg/day given in two or three divided doses. Dosage should be increased by no more than 0.25 to 0.5 mg every third day until a daily maintenance dose of 0.1 to 0.2 mg/kg of body weight has been reached unless seizures are controlled or side effects preclude further increase. Whenever possible, the daily dose should be divided into three equal doses. If doses are not equally divided, the largest dose should be given before retiring.

HOW SUPPLIED: The 0.5 mg tablets are yellow, round, scored, biconvex tablets debossed with **M** on one side and with **C** and **13** on the other side. They are available as follows:

NDC 0378-1910-01
bottles of 100 tablets

NDC 0378-1910-10
bottles of 1000 tablets

The 1 mg tablets are light green, round, scored, biconvex tablets debossed with **M** on one side and with **C** and **14** on the other side. They are available as follows:

NDC 0378-1912-01
bottles of 100 tablets

NDC 0378-1912-10
bottles of 1000 tablets

The 2 mg tablets are white, round, scored, biconvex tablets debossed with **M** on one side and with **C** and **15** on the other side. They are available as follows:

NDC 0378-1914-01
bottles of 100 tablets

NDC 0378-1914-05
bottles of 500 tablets

STORE AT CONTROLLED ROOM TEMPERATURE 15°-30°C (59°-86°F).

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

REVISED AUGUST 1998
CZPM:R3

MYLAN PHARMACEUTICALS INC.

CLONAZEPAM TABLETS, USP 1 mg

ANDA 75-150

N 3 0378-1912-10 5

MYLAN®

NDC 0378-1912-10

CIV

CLONAZEPAM TABLETS, USP 1 mg

1000 TABLETS

N 3 0378-1912-10 5

MYLAN®

NDC 0378-1912-10

CIV

CLONAZEPAM TABLETS, USP 1 mg

1000 TABLETS

N 3 0378-1912-10 5

MYLAN®

NDC 0378-1912-10

CIV

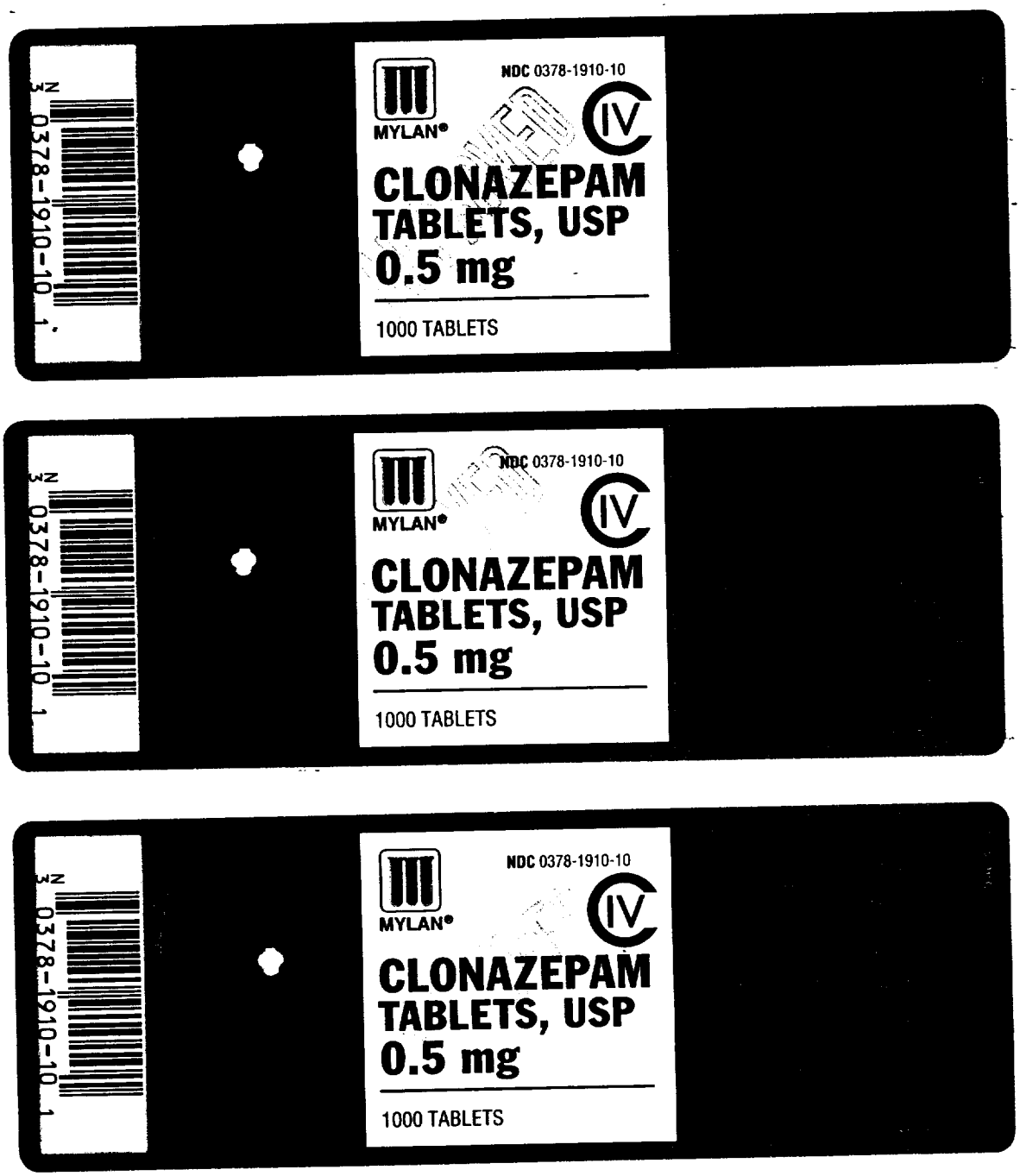
CLONAZEPAM TABLETS, USP 1 mg

1000 TABLETS

MYLAN PHARMACEUTICALS INC.

CLONAZEPAM TABLETS, USP 0.5 mg

ANDA 75-150



MYLAN PHARMACEUTICALS INC.

CLONAZEPAM TABLETS, USP 2 mg

ANDA 75-150

N 3 0378-1914-01 7

MYLAN®

NDC 0378-1914-01

CIV

CLONAZEPAM
TABLETS, USP
2 mg

100 TABLETS

N 3 0378-1914-01 7

MYLAN®

NDC 0378-1914-01

CIV

CLONAZEPAM
TABLETS, USP
2 mg

100 TABLETS

N 3 0378-1914-01 7

MYLAN®

NDC 0378-1914-01

CIV

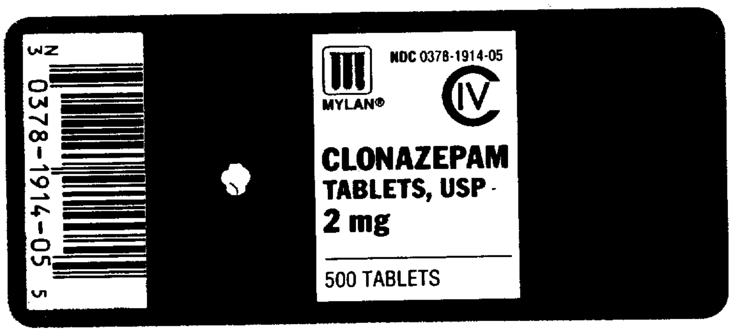
CLONAZEPAM
TABLETS, USP
2 mg

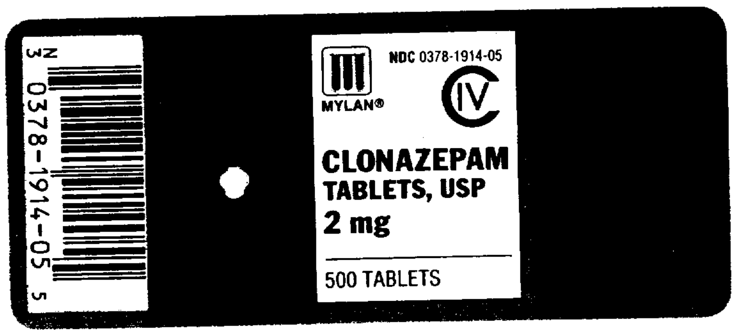
100 TABLETS

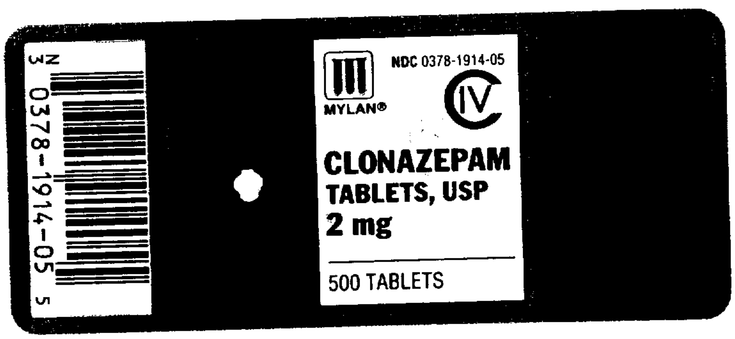
MYLAN PHARMACEUTICALS INC.

CLONAZEPAM TABLETS, USP 2 mg

ANDA 75-150







CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75150

CHEMISTRY REVIEW(S)

DIVISION REVIEW SUMMARY

ANDA: 75-150

DRUG PRODUCT: Clonazepam Tablets, USP

FIRM: Mylan Pharmaceuticals, Inc.

DOSAGE FORM: Tablets

STRENGTH: 0.5 mg, 1 mg, 2 mg

CGMP STATEMENT/EIR UPDATE STATUS:
Pending

BIO INFORMATION:
The Division of Bioequivalence have determined that the biostatus is acceptable as of 11/18/97 by M. Makary.

VALIDATION-(DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S)
The chromatographic method for assaying the drug substance is in accordance with USP XXII. The Related Compounds testing performed is also in accordance with USP 23 methods.

STABILITY-ARE CONTAINERS USED IN THE STUDY IDENTICAL TO THOSE USED IN THE CONTAINER SECTION?
The applicant includes a stability protocol beginning on page 2784. The post approval protocol is included beginning on page 2816. The applicant will test at 27.5°C ± 2.5°C and ambient humidity. Testing stations are in accordance with FDA Guidelines. The firm will test for:

Test	Specification
Assay	%
Dissolution	NLT % (Q) in 60 minutes
*Related Compounds	NMT % 3-amino-4-(2-chlorophenyl)-6-nitrocarbostyril NMT % 2-amino-2'-chloro-5-nitrobenzophenone NMT % Any Individual Unknown Impurity NMT % Total Unknown Impurities

Appearance	Visual check
**Hardness	6-15 kp
**Friability	NMT %
**Loss on Drying	NMT %

*Revised upon request.
**Added upon request.

The firm included 3 months of accelerated stability data (40°C, 75% RH) for lots #2C001N, 2C002N and 2C003N. Also included is a stability commitment to place the first 3 lots on stability and a minimum of one lot annually therafter in the largest and smallest package sizes.

LABELING
The labeling review is acceptable 9/15/98.

STERILIZATION VALIDATION
The product is not sterilized.

SIZE OF DEMONSTRATION BATCH
A description of the manufacturing process is included beginning on page 2134. Included are flow diagrams for the manufacture of Clonazepam 2% Intermediate, and Clonzepam tablets 0.5 mg, 1 mg, and 2 mg. The process is a dry blend. The procedure involves manufacture which is prepared by . The intermediate is prepared

The tablets are manufactured by

The blank batch records are included on pages 2146-2256. The firm's exhibit batch sizes and proposed production lot sizes are listed as follows:

Clonazepam Intermediate
kg (lot # R&D-1386) and kg (proposed)

0.5 mg tablets
tablets (lot # 2C001N) and tablets (proposed)

1.0 mg tablets
tablets (lot #2C002N) and tablets (proposed)

2.0 mg tablets
tablets (lot #2C003N) and tablets (proposed)

The executed batch records are included beginning on page 2275. Batch reconciliation data indicated that for lot #2C001N (0.5 mg) % material was accounted for and tablets were packaged % packaging accountability). Lot #2C002N (1.0 mg tablets) showed % accounted for and tablets were packaged % packaging accountability). Lot #2C003N (2 mg tablets) showed % acounted for and tablets packaged % packaging accountability.

PROPOSED PRODUCTION BATCH-MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?
The manufacturing process will be the same for the production batch as the stability batch.

RECOMMENDATION:
Approve

SIGNATURE: /S/ DATE: September 16, 1998
9/22/98

1. CHEMIST'S REVIEW NO.3

2. ANDA # 75-150

3. NAME AND ADDRESS OF APPLICANT

Mylan Pharmaceuticals, Inc.
Attention: Frank R. Sisto
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

4. LEGAL BASIS FOR SUBMISSION
Page 6 includes a legal basis for submission. Patent Certification information is included on pages 8-15.

5. SUPPLEMENT(s)
NA

6. PROPRIETARY NAME
Klonopin Tablets

7. NONPROPRIETARY NAME
Clonazepam Tablets, USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:
NA

9. AMENDMENTS AND OTHER DATES:

Original Submission	June 27, 1997
Acknowledgement Letter	August 15, 1997
FDA Deficiency Letter	December 9, 1997
Amendment Response	March 26, 1998
FDA Fax Deficiency Letter	August 6, 1998
Amendment Response	August 24, 1998

10. PHARMACOLOGICAL CATEGORY
Antiseizure

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)
NDA #17-533

DMF	DMF
DMF	DMF
DMF	DMF
DMF	DMF
DMF	DMF
DMF	DMF

13. DOSAGE FORM
Tablets

14. POTENCY
0.5 mg, 1 mg, 2 mg

15. CHEMICAL NAME AND STRUCTURE
2 H-1,4-Benzodiazepin-2-one, 5-(2-chlorophenyl)-1,3-dihydro-7-nitro-5-(O-Chlorophenyl)1,3-dihydro-7-nitro-2H-1,4,-benzodiazepin-2-one

16. RECORDS AND REPORTS
NA

17. COMMENTS
All deficiencies have been resolved satisfactorily.

18. CONCLUSIONS AND RECOMMENDATIONS
This application is approvable.

19. REVIEWER: Karen A. Bernard, Ph.D.
DATE COMPLETED: September 17, 1998

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75150

BIOEQUIVALENCY REVIEW(S)

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-150 APPLICANT: Mylan Pharmaceticals, Inc.

DRUG PRODUCT: Clonazepam Tablets USP, 0.5 mg, 1 mg and 2 mg.

The Division of Bioequivalence has completed its review and has no further questions at this time.

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in U.S.P. 23.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Rabindra N. Patnaik, Ph.D.
Acting Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Clonazepam
0.5, 1 and 2 mg Tablets
ANDA #75-150
Reviewer: Moheb H. Makary
WP 75150SDW.697

Mylan Pharmaceuticals Inc.
Morgantwon, WV
Submission Date:
June 27, 1997
September 3, 1997

Review of a Bioequivalence Study, Dissolution Testing and Waiver Requests

I. Objective:

Mylan Pharmaceuticals Inc., has submitted results of a comparative bioequivalence study and dissolution testing conducted on its test product, Clonazepam Tablet, 1 mg, and Klonopin[R] Tablet (Clonazepam), 1 mg, manufactured by Roche, as the listed reference product. The firm has requested waivers of in vivo study requirements for its 0.5 mg and 2 mg strengths.

II. Introduction:

Clonazepam is a member of the older 1,4 ring class of benzodiazepine and has been used clinically as an anticonvulsant. Single oral dose of Clonazepam to humans gave maximum blood levels of drug, in most cases, within one to two hours. The half-life of the parent compound varied from approximately 18 to 50 hours, and the major route of excretion was in the urine. In humans, five metabolites have been identified. In general, the biotransformation of clonazepam followed two pathways: oxidative hydroxylation at the C-3 position and reduction of the 7-nitro function to form 7-amino and/or 7-acetyl-amino derivatives. The metabolites of clonazepam have no significant pharmacologic activity.

The most frequently occurring side effect of clonazepam is referable to CNS depression. Experience to date has shown that drowsiness has occurred in approximately 50% of patients and ataxia in approximately 30%. In some cases, these may diminish with time; behavior problems have been noted in approximately 25% of patients.

Clonazepam is available commercially as Klonopin[R] oral tablets, 0.5 mg, 1 mg and 2 mg manufactured by Hoffmann-La Roche Inc. The recommended initial dose of clonazepam for adults should not exceed 1.5 mg/day divided into three doses. The largest dose should be given at bedtime if doses are not equally divided. Dosage may be increased in increments of 0.5 to 1 mg every three days until seizures are adequately controlled. Maximum recommended daily dose is 20 mg.

III. Protocol #CLON-9683 For Single-Dose, Two-Way Crossover

Bioavailability Study of Clonazepam 1 mg Tablet Under Fasting Conditions:

Study site:

Analytical site:

Sponsor: Mylan Pharmaceuticals Inc.
Morgantwon, WV

Investigators:

Study design: Single-dose, randomized, 2-way crossover study, under fasting conditions

Subjects: Thirty-six (36) healthy adult male volunteers enrolled and thirty-three (33) subjects completed the study.

Inclusion criteria: The subjects were between 18 and 45 years old. They were within 10% of their ideal weights (Table of "Desirable Weights of Adults", Metropolitan Life Insurance Company, 1983). Each subject received a complete physical examination and laboratory tests of hematopoietic, hepatic and renal functions. Only medically healthy subjects with clinically normal laboratory profiles and negative urine drug and alcohol prior to each phase were enrolled in the study.

Exclusions: Subjects with history or presence of:
-cardiovascular, pulmonary, hepatic, renal, hematological or significant gastrointestinal disease;
-hypersensitivity or idiosyncratic reaction to clonazepam or any other benzodiazepines, were excluded from the study.

Restrictions: The consumption of alcohol beverages, xanthine and caffeine containing foods were prohibited for 48 hours, before dosing and throughout the period of samples collection. Subjects were instructed to take no medication (including OTC) within 14 days prior to start the study.

Dose and treatments: All subjects completed an overnight fast before any of the following drug treatments:

and 3.9% lower, respectively, than their reference product values. The differences were not statistically significant. The 90% confidence intervals were within the acceptable range of 80-125% for log-transformed AUC(0-t), AUCinf.
And Cpeak.

2. Clonazepam plasma levels peaked at 2 and 2.5 hours for the test and the reference products, respectively, following their administration under fasting conditions.

V. Formulations:

Mylan's comparative formulations for its Clonazepam Tablets 0.5 mg 1 mg and 2 mg are shown in Table III.

VI. In Vitro Dissolution Testing:

USP Method	
Method:	USP 23 apparatus II (paddle) at 100 rpm
Medium:	900 mL of deaerated water @ 37°C
Number of Tablets:	12
Test Products:	Mylan's Clonazepam
	0.5 mg Tablets, lot #2C001N
	1 mg Tablets, lot #2C002N
	2 mg Tablets, lot #2C003N
Reference Products:	Roche's Klonopin®
	0.5 mg Tablets, lot #1917
	1 mg Tablets, lot #2202
	2 mg Tablets, lot #3063
Specifications:	NLT % in 60 minutes

Dissolution testing results are shown in Table VI.

VII. Comments:

1. The confidence intervals for LNAUC(0-t), LNAUCinf and LNCpeak are within the acceptable range of % under fasting conditions.

2. The in vitro dissolution testing for the test products, 0.50 mg, 1 mg and 2 mg strengths, is acceptable.

3. The formulations for the 0.5 mg and 2 mg strengths are proportionally similar to the 1 mg strength of the test product.

VIII. Recommendations:

1. The single-dose bioequivalence study under fasting conditions conducted by Mylan Pharmaceuticals Inc., on its Clonazepam 1 mg Tablet, lot #2C002N, comparing it to Klonopin® 1 mg Tablet manufactured by Roche Pharma, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Mylan's

Clonazepam Tablet, 1 mg is bioequivalent to the reference product, Klonopin[R] 1 mg Tablet manufactured by Roche Pharma.

2. The dissolution testing conducted by Mylan Pharmaceuticals Inc., on its Clonazepam 0.5 mg Tablets, lot #2C001N, 1 mg lot #2C002N and 2 mg Tablets, lot #2C003N, comparing them with the respective strengths of Roche's Klonopin[R] 0.5 mg, 1 mg and 2 mg Tablets is acceptable. The formulations for the 0.5 mg and 2 mg strengths are proportionally similar to the 1 mg strength of the test product which underwent acceptable bioequivalence testing. Waivers of in vivo bioequivalence study requirements for the 0.5 mg and 2 mg tablets of the test products are granted. The Division of Bioequivalence deems Clonazepam Tablets 0.5 mg and 2 mg, manufactured by Mylan Pharmaceuticals Inc., to be bioequivalent to Klonopin[R] Tablets 0.5 mg and 2 mg, respectively, manufactured by Roche Pharma.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of deaerated water at 37°C using USP 23 apparatus II (paddle) at 100 rpm. The test product should meet the following specification:

> Not less than % of the labeled amount of the drug in the dosage form is dissolved in 60 minutes.

The firm should be informed of the above recommendations

/S/

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE /S/ Date: 11/18/97

Concur: /S/ Date: 11/18/97
Rabindra Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

Mmakary/9-4-97, 11-17-97 wp 75150SDW.697
cc: ANDA #75-150, original, HFD-658 (Makary), Drug File, Division File.

Table IV. In Vitro Dissolution Testing

Drug (Generic Name):Clonazepam
Dose Strength: 0.5 mg, 1 mg and 2 mg
ANDA No.: 75-150
Firm: Mylan
Submission Date: June 27, 1997
File Name: 75150SDW.697

I. Conditions for Dissolution Testing:

USP 23 Basket: Paddle: X RPM: 100
No. Units Tested: 12
Medium: 900 mL of water
Specifications: NLT % in 60 minutes
Reference Drug: Klonopin
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot #2C001N Strength(mg) 0.5			Reference Product Lot # 1917 Strength(mg) 0.5		
	Mean %	Range	%CV	Mean %	Range	%CV
15	75		3.0	78		1.6
30	87		1.7	90		1.1
45	91		2.0	94		1.2
60	92		1.3	95		1.2

Sampling Times (Minutes)	Test Product Lot # 2C002N Strength(mg) 1			Reference Product Lot # 2202 Strength(mg) 1		
	Mean %	Range	%CV	Mean %	Range	%CV
15	75		2.0	79		3.1
30	88		1.6	92		0.8
45	91		1.4	96		1.1
60	94		1.3	98		1.2

Sampling Times (Minutes)	Test Product Lot # 2C003N Strength(mg) 2			Reference Product Lot # 3063 Strength(mg) 2		
	Mean %	Range	%CV	Mean %	Range	%CV
15	70		2.4	72		5.3
30	85		0.9	88		1.3
45	91		1.3	94		1.1
60	92		0.6	96		1.1

Test product:	A. 1X1 mg clonazepam, (Mylan Pharmaceuticals Inc.), lot #2C002N, Exp. N/A. lot size Tablets, Content uniformity % (CV=1.2%), potency %.
Reference product:	B. 1x1 mg Klonopin® Tablet (Roche Pharma Inc.), lot #2202, Exp. 9/99, content uniformity % (CV=1.7%), potency %.
Food and fluid intake:	Single, oral 1 mg (1 tablet) dose administered with 240 mL of water. Meals were provided at 5 and 10 hours after dosing. Fluids were allowed one hour before until one hour after dosing.
Blood samples:	Blood samples were collected at: 0, 0.25, 0.5, 0.75, 1, 1.50, 2.00, 2.50, 3, 3.5, 4.00, 6.00, 8.00, 12.00, 24.00, 36.00, 48.00, 72.00, 96.00, 120.00, 144.00 and 168.00. Plasma samples were stored frozen at -12°C pending assay.
Washout period:	Three weeks

Assay methodology:

Statistical Analysis:

ANOVA was performed at an alpha = 0.05 using the SAS-GLM. The 90% confidence intervals (2 one-sided t-test method) were calculated for LNAUC(0-t), LNAUCinf and LNCpeak.

IV. In Vivo Results:

Thirty-six healthy male volunteers enrolled in the study, three subjects did not complete the crossover. Subject #5 elected to withdraw from the study prior to period 2 dosing for personal reasons, subject #12 experienced the onset of intermittent diarrhea, vomiting and upset stomach between 18.9 and 19.9 days after period 1 dosing. The subject was withdrawn 22 minutes before period 2 dosing by the medical designate due to these medical events. Subject #32 experienced a blocked left ear 13.5 days after period 1 dosing. The subject was withdrawn 2 hours before period 2 dosing by the medical designate due to this medical event. Thus, a total of 33 subjects completed the study. Fifty-two adverse events which were probably or possibly related to the study drug were reported. All adverse events are shown in Table I. The results indicate that the incidence of adverse experiences were similar between the test and reference products.

The plasma concentrations and pharmacokinetic parameters are

summarized in Table II.

Table II

Mean Plasma Concentrations And Pharmacokinetic Parameters
Following An Oral Dose of 1 mg (1mg Tablet)
Clonazepam Under Fasting Conditions
(N=33)

Time (hr)	Mylan Test product Lot #2C002N ng/mL (C.V.)	Roche Pharma Reference product Lot #2202 ng/mL (C.V.)
0		
0.25	(399.4)	(412.0)
0.50	(85.5)	(93.5)
0.75	(54.9)	(52.9)
1	(41.6)	(39.3)
1.50	(28.3)	(32.2)
2.00	(21.2)	(27.8)
2.50	(16.8)	(22.1)
3	(16.0)	(21.7)
3.5	(16.4)	(21.6)
4	(15.7)	(18.2)
6.0	(16.6)	(16.3)
8	(14.8)	(17.5)
12	(17.1)	(16.0)
24	(19.9)	(17.1)
36	(17.3)	(21.2)
48	(17.2)	(21.2)
72	(23.6)	(24.2)
96	(28.9)	(30.5)
120	(34.8)	(34.6)
144	(39.7)	(39.3)
168	(53.4)	(61.3)

	Test	Reference	90% CI
AUC(0-t) (ng.hr/mL)	272.0(17.8)	274.2(18.3)	
AUCinf (ng.hr/mL)	287.7(19.2)	288.9(19.6)	
Cpeak (ng/mL)	7.4(17.2)	7.7(21.5)	
TMAX (hr)	2.61	2.56	
Kel (1/hr)	0.02	0.02	
Half-life (hr)	39.19	38.35	
LNAUC(0-t)			96-102%
LNAUCinf			96-102%
LNCMAX			92-103%

1. Mylan's test product had an AUC(0-t) of 272.0 ng.hr/mL, AUCinf of 287.7 ng.hr/mL and Cpeak of 7.4 ng/mL, which were 0.8%, 0.4%

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75150

ADMINISTRATIVE DOCUMENTS

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

AND Number: **75-150** Date of Submission: **March 26, 1998**

Applicant's Name: **Mylan Pharmaceuticals, Inc.**

Established Name: **Clonazepam Tablets USP, 0.5 mg, 1 mg and 2 mg.**

Labeling Deficiencies:

1. CONTAINERS - 100's & 1000's (0.5 mg & 1 mg)
   100's & 500's (2 mg)

   Satisfactory in final print.

2. INSERT

   CLINICAL PHARMACOLOGY

   Pharmacodynamics - Delete from the first sentence.

Please revise your insert labeling, as instructed above, and submit in final print.

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 your last submission with all differences annotated and explained.

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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

AND Number: **75-150** Date of Submission: **June 27, 1997**

Applicant's Name: **Mylan Pharmaceuticals, Inc.**

Established Name: **Clonazepam Tablets USP, 0.5 mg, 1 mg and 2 mg.**

Labeling Deficiencies:

1. CONTAINERS - 100's & 1000's (0.5 mg & 1 mg)
   100's & 500's (2 mg)

   Please assure that the established name and expression of the strengths appear prominently on the label.

2. INSERT

   a. DESCRIPTION

      i. First paragraph - Revise the first two sentences to read as follows:

         Clonazepam is a benzodiazepine and chemically designated as 5-(*o*-Chlorophenyl)- ... [delete

      ii. We encourage you to revise the chemical name to be same as the second name appearing in the official monograph for clonazepam tablets in USP 23. In addition, include the molecular formula.

      iii. Second paragraph

         A) First sentence - Revise to read as follows:

            Each tablet, for oral administration contains 0.5 mg, 1 mg, or 2 mg of clonazepam. In addition, each tablet contains the following inactive ingredients: anhydrous ... lauryl

sulfate.

B) Second sentence:

Additionally, the 0.5 mg tablets contain ...

C) Last sentence:

The 1 mg tablets contain ...

b. WARNINGS

i. Pregnancy Risks (Animal Findings) -

A) First sentence:

(1) Delete the terminal zeros. [e.g. "1 mg" rather than

(2) ... 20 mg/day on a mg/m^2 basis) during ... [delete

(B) Last sentence:

... 20 mg/day on a mg/m^2 basis). [delete

ii. General concerns and consideration About Anticonvulsants - Second paragraph:

Relocate this paragraph to be the second sentence of the first paragraph.

iii. Advice Regarding the use of clonazepam in Women of Childbearing Potential - Last paragraph, penultimate sentence:

... taking this drug, the patient ... [add a "comma"]

c. PRECAUTIONS

i. Carcinogenesis, Mutagenesis, Impairment of Fertility - Last paragraph:

... 20 mg/day on a mg/m^2 basis), there ... [delete

ii. Pediatric Use

... important in patients (see **INDICATIONS** and ...).

d. ADVERSE REACTIONS (Seizure Disorder)

i. Delete after the section heading.

ii. Secod sentence:

Experience has shown that ...

e. DOSAGE AND ADMINISTRATION

i. Delete after the section heading.

ii. First paragraph, first sentence:

... dose for adults should not .. [delete

f. HOW SUPPLIED

i. First paragraph:

... yellow, scored, biconvex ... one side and with **C** and **13** on the other side. They are ...

ii. Second and third paragraphs:

A) Delete the terminal zeros.

B) Refer to the comment under the first paragraph.

Please revise your container labels and insert labeling, as instructed above, and submit in final print.

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 your last submission with all differences annotated and explained.

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75150

CORRESPONDENCE

ANDA 75-150

Mylan Pharmaceuticals Inc.
Attention: Frank R. Sisto
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, West Virginia 26504-4310

AUG 15 1997

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Clonazepam Tablets USP, 0.5 mg, 1 mg, and 2 mg

DATE OF APPLICATION: June 27, 1997

DATE OF RECEIPT: June 30, 1997

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Kassandra Sherrod
Project Manager
(301) 827-5849

Sincerely yours,

/S/

Jerry Phillips 8/14/97
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

505(j)(2) OK
8/12/97
Gregory S. Davis

JUN 27 1997

ELECTRONIC DATA ENCLOSED
BIOEQUIVALENCE DATA ENCLOSED

Office of Generic Drugs, CDER, FDA
Douglas L. Sporn Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: CLONAZEPAM TABLETS, USP
0.5MG, 1MG, AND 2MG

Dear Mr. Sporn:

Pursuant to section 505(j) of the Federal Food, Drug and Cosmetic Act and 21 CFR §314.92 and §314.94, we submit the enclosed abbreviated new drug application for:

Proprietary Name: None
Established Name: Clonazepam Tablets, USP
This application consists of a total of 15 volumes.
Archival Copy - 6 volumes.
Review Copy - 7 volumes.
Technical Section For Chemistry - 3 volumes.
Technical Section For Pharmacokinetics - 4 volumes.
Analytical Methods - 2 extra copies; 1 volume each.
NOTE: The Technical Section for Pharmacokinetics of the review copy and the archival copy each contain a data diskette for the bioequivalence studies conducted in support of this application. An electronic data set, using the Office of Generic Drug's new EVA software program, is currently being prepared and will be submitted as an amendment to this application as soon as it becomes available.

This application provides for the manufacture of Clonazepam Tablets, USP 0.5mg, 1mg, and 2mg. All operations in the manufacture, packaging, and labeling of the drug product are performed by Mylan Pharmaceuticals Inc., 781 Chestnut Ridge Road, Morgantown, WV 26505-2730.

As required by 21 CFR §314.94(d)(5) we certify that a true copy of the technical sections of this application, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office. The following Table of Contents and Reader's Guide detail the documentation submitted in support of this application.

All correspondence regarding this application should be directed to the attention of the undersigned at Mylan Pharmaceuticals Inc., P.O. Box 4310, 781 Chestnut Ridge Road, Morgantown WV, 26504-4310, or via facsimile at (304) 285-6407.

RECEIVED
JUN 30 1997
GENERIC DRUGS

Sincerely,

Frank R. Sisto
Executive Director
Regulatory Affairs

Department/Room
Accounting (304) 285-6403
Administration (304) 599-7284
Business Development (304) 599-7284
Human Resources (304) 598-5406
Information Systems (304) 285-6404
Label Control (800) 848-0463
Legal Services (304) 598-5408
Maintenance & Engineering (304) 598-5411
Medical Unit (304) 598-5445
Purchasing (304) 598-5401
Quality Control (304) 598-5407
Research & Development (304) 285-6409
Sales & Marketing (304) 598-3232

[RDLIB.ANDA.CLONAZEPAM]SECTIONS-01THRU07

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

ORIG AMENDMENT

NDA

AUG 24 1998

Office of Generic Drugs, CDER, FDA
Douglas L. Sporn, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

FACSIMILE AMENDMENT
(CMC Information Enclosed)

RE: CLONAZEPAM TABLETS, USP 0.5MG, 1MG AND 2MG
ANDA #75-150
RESPONSE TO AGENCY CORRESPONDENCE DATED AUGUST 6, 1998

Dear Mr. Sporn:

Reference is made to the Abbreviated New Drug Application identified above, which is currently under review, and to the comments from the Agency pertaining to this application which were provided to Mylan in a facsimile dated August 6, 1998. In response to the Agency's comments of August 6, Mylan wishes to amend this application as follows.

A. REGARDING CHEMISTRY ISSUES

FDA COMMENT 1. Regarding your response concerning the addition of a Moisture specification into your finished drug product and stability testing protocol, we have the following comments:

> We note that you intend to utilize a desiccant in the finished product packaging, although you have provided no stability data measurements for Moisture. We still believe that Moisture testing of the finished Clonazepam Tablets is important. We do not believe that you have provided sufficient justification for not including this testing in your finished drug product or stability testing protocol, regardless of the fact that a dry blend operation is utilized in the manufacture of the drug product.
>
> In addition, it is also noted that you do not perform an LOD test as an in-process control measurement of the Clonazepam intermediate % or the final blend.

RECEIVED

AUG 25 1998

GENERIC DRUGS

R:\ANDA\CLONAZEPAM\AGENCY-LETTER-DATED-080698.WPD

Department—Fax Numbers		Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Accounting	(304) 285-6403	Label Control	(800) 848-0463	Quality Control	(304) 598-5407
Administration	(304) 599-7284	Legal Services	(304) 598-5408	Research & Development	(304) 285-6409
Business Development	(304) 599-7284	Maintenance & Engineering	(304) 598-5411	Sales & Marketing	(304) 598-3232
Human Resources	(304) 598-5406	Medical Unit	(304) 598-5445		

Since degradation of Clonazepam occurs principally via a process, we are again requesting that you establish a reasonable specification for Moisture in your finished product testing and in your stability testing protocol. Also, we note that you have controlled the two main degradation products due to hydrolysis. If you would prefer, you may wish to provide previously collected data including Moisture measurements of the drug product generated during stability testing that will fully justify your request for not including Moisture testing in this drug product.

Also, since you propose a 6 month holding time for the intermediate, please provide information regarding the storage of the blended material with respect to moisture accumulation.

MYLAN RESPONSE: As requested by the Agency, Mylan has established a moisture test for the finished product and stability testing of Clonazepam Tablets, USP 0.5mg, 1mg and 2mg with a limit of Not More Than %. Mylan established this specification based on the calculated maximum theoretical moisture content of each of the excipients and active contained in the tablets which was determined to be about %. Moisture testing was also performed on 18 month room temperature stability samples as well as 3 month 40°C/75% RH samples stored at ambient room temperature conditions subsequent to the 3 month stressed conditions. The data generated, provided in Attachment 1, supports the established specification. The procedure, revised finished product specifications for each strength and revised post-approval stability protocols for each strength are included in Attachments 2, 3 and 4, respectively.

Regarding Mylan's proposed 6 month holding time for the Clonazepam 2% Intermediate, at this time moisture data for the blended material is unavailable. However, as the 2% Intermediate is common to all three strengths, it is necessary to define a suitable holding period. Therefore, Mylan commits to a storage time limit of 3 months for the Clonazepam 2% Intermediate. Should Mylan decide to extend the holding period, the appropriate stability data to support this extended holding period will be generated and submitted in a prior approval supplement.

B. REGARDING LABELING ISSUES

MYLAN RESPONSE: Attachment 7 contains twelve (12) copies of the following final printed package outsert for Clonazepam Tablets, USP.

PACKAGE OUTSERT

Code - CZPM:R3; revised AUGUST 1998

The enclosed outsert incorporates the revisions requested in the Agency's letter dated August 6, 1998. A copy of this letter is provided in Attachment 5 for the convenience of the reviewer.

In order to facilitate the review of this outsert and in accordance with 21 CFR 314.94(a)(8)(iv), Attachment 6 contains a side-by-side comparison of the final printed outsert to the outsert that was previously submitted. It is noted that prior to approval of this application the agency reserves the right to request further changes in the Mylan labeling based upon the changes in the approved labeling of the listed drug or upon further review of the application.

As previously noted, a copy of the Agency correspondence dated August 6, 1998 is included in Attachment 5, for the convenience of the reviewer.

Pursuant to 21 CFR 314.96(b), we certify that a true copy of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6600 or via facsimile at (304) 285-6407.

Sincerely,

Frank R. Sisto
Vice President
Regulatory Affairs

FRS/tlr

enclosures

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

MAR 19 1998

Office of Generic Drugs, CDER, FDA
Douglas L. Sporn, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

BIOEQUIVALENCE AMENDMENT

RE: CLONAZEPAM TABLETS, USP
0.5MG, 1MG, AND 2MG
ANDA #75-150
RESPONSE TO AGENCY CORRESPONDENCE DATED DECEMBER 9, 1997

Dear Mr. Sporn:

Reference is made to the ANDA identified above, which is currently under review, and to the December 9, 1997 letter pertaining to this application which was forwarded to Mylan from the Office of Generic Drugs' Division of Bioequivalence. In response to the December 9 correspondence, Mylan wishes to amend the application as follows:

A. REGARDING BIOEQUIVALENCE ISSUES:

FDA COMMENT 1. The Division of Bioequivalence has completed its review and has no further questions at this time.

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in U.S.P. 23.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Department—Fax Numbers		Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
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Human Resources	(304) 598-5406	Medical Unit	(304) 598-5445		

MYLAN RESPONSE: The dissolution testing requested by the Division of Bioequivalence has already been incorporated into Mylan's stability and quality control programs. This testing is identical to that which was previously proposed in the original ANDA for the above referenced product which was submitted on June 27, 1997.

It is also acknowledged and understood that the bioequivalency comments expressed in the letter dated December 9, 1997 are preliminary and may be revised after review of the entire application.

For your reference, a copy of the Agency correspondence dated December 9, 1997 is enclosed.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6600 or via facsimile at (304) 285-6407.

Sincerely,

Frank R. Sisto
Executive Director
Regulatory Affairs

FRS/tlm

enclosures