CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074979

Trade Name : CLONAZEPAM TABLETS USP

Generic Name: Clonazepam Tablets USP 0.5mg, 1.0mg and 2.0mg

Sponsor : Eon Labs Manufacturing, Inc.

Approval Date: August 29, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074979

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074979

APPROVAL LETTER

ANDA 74-979

AUG 29 1997

Eon Labs Manufacturing, Inc.
Attention: Sadie M. Ciganek
227-15 North Conduit Avenue
Laurelton, NY 11413

Dear Madam:

This is in reference to your abbreviated new drug application dated October 7, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Clonazepam Tablets USP, 0.5 mg, 1.0 mg, and 2.0 mg.

Reference is also made to your amendments dated April 8, June 20, July 14 and August 25 and 27, 1997.

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, 1.0 mg and 2.0 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Klonopin® Tablets, 0.5 mg, 1.0 mg and 2.0 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. 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-240). 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-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

8/29/97

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074979

FINAL PRINTED LABELING

MARGO

FINAL PRINTED LABEL

Lot No.:
Exp. Date:

USUAL DOSAGE: See accompanying literature for complete prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F).

This is a bulk package. Dispense in tight, light-resistant containers as defined in the USP, with a child-resistant closure, as required.

Issued 03/97

NDC 0185-0063-01

Clonazepam Tablets, USP C IV

0.5 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 Tablets

Eon Labs

Each tablet contains:
Clonazepam ..... 0.5 mg

KEEP TIGHTLY CLOSED.

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

APPROVED

Lot No.:
Exp. Date:

USUAL DOSAGE: See accompanying literature for complete prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F).

This is a bulk package. Dispense in tight, light-resistant containers as defined in the USP, with a child-resistant closure, as required.

Issued 03/97

NDC 0185-0063-05

Clonazepam Tablets, USP C IV

0.5 mg

CAUTION: Federal law prohibits dispensing without prescription.

500 Tablets

Eon Labs

Each tablet contains:
Clonazepam ..... 0.5 mg

KEEP TIGHTLY CLOSED.

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

APPROVED

Lot No.:
Exp. Date:

USUAL DOSAGE: See accompanying literature for complete prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F).

This is a bulk package. Dispense in tight, light-resistant containers as defined in the USP, with a child-resistant closure, as required.

Issued 03/97

NDC 0185-0063-10

Clonazepam Tablets, USP C IV

0.5 mg

CAUTION: Federal law prohibits dispensing without prescription.

1000 Tablets

Eon Labs

Each tablet contains:
Clonazepam ..... 0.5 mg

KEEP TIGHTLY CLOSED.

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

APPROVED

FINAL PRINTED LABEL

Lot No.:
Exp. Date:

USUAL DOSAGE: See accompanying literature for complete prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F).

This is a bulk package. Dispense in tight, light-resistant containers as defined in the USP, with a child-resistant closure, as required.

Issued 03/97

NDC 0185-0064-01

Clonazepam Tablets, USP C IV

1 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 Tablets

Eon Labs

Each tablet contains:
Clonazepam ..... 1 mg

KEEP TIGHTLY CLOSED.

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

Lot No.:
Exp. Date:

USUAL DOSAGE: See accompanying literature for complete prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F).

This is a bulk package. Dispense in tight, light-resistant containers as defined in the USP, with a child-resistant closure, as required.

Issued 03/97

NDC 0185-0064-05

Clonazepam Tablets, USP C IV

1 mg

CAUTION: Federal law prohibits dispensing without prescription.

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Eon Labs

Each tablet contains:
Clonazepam ..... 1 mg

KEEP TIGHTLY CLOSED.

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

Lot No.:
Exp. Date:

USUAL DOSAGE: See accompanying literature for complete prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F).

This is a bulk package. Dispense in tight, light-resistant containers as defined in the USP, with a child-resistant closure, as required.

Issued 03/97

NDC 0185-0064-10

Clonazepam Tablets, USP C IV

1 mg

CAUTION: Federal law prohibits dispensing without prescription.

1000 Tablets

Eon Labs

Each tablet contains:
Clonazepam ..... 1 mg

KEEP TIGHTLY CLOSED.

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

N. ARGO

FINAL PRINTED LABEL

Lot No.:
Exp. Date:

USUAL DOSAGE: See accompanying literature for complete prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F).

This is a bulk package. Dispense in tight, light-resistant containers as defined in the USP, with a child-resistant closure, as required.

Issued 03/97

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Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

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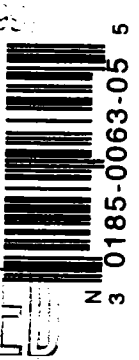
Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413



Lot No.:
Exp. Date:

USUAL DOSAGE: See accompanying literature for complete prescribing information.

Store at controlled room temperature 15°-30°C (59°-86°F).

This is a bulk package. Dispense in tight, light-resistant containers as defined in the USP, with a child-resistant closure, as required.

Issued 03/97

NDC 0185-0063-10

Clonazepam Tablets, USP C IV

0.5 mg

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Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

CLONAZEPAM TABLETS, USP C IV

CLONAZEPAM TABLETS, USP C IV

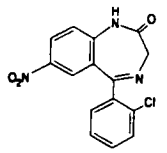
REV07/97

CLONAZEPAM TABLETS, USP C IV

DESCRIPTION

Clonazepam tablets USP, for oral administration, contain 0.5 mg, 1 mg or 2 mg clonazepam. In addition, each tablet also contains the following inactive ingredients: anhydrous lactose, corn starch, magnesium stearate, and microcrystalline cellulose with the following colorants: 0.5 mg-D&C Yellow No. 10 Aluminum Lake; 1 mg-FD&C Blue No. 1 Aluminum Lake.

Chemically, clonazepam is 5-(*o*-chlorophenyl)-1,3-dihydro-7-nitro-2*H*-1,4-benzodiazepin-2-one. It is a light yellow crystalline powder, insoluble in water, sparingly soluble in acetone and chloroform and slightly soluble in alcohol. It has a molecular weight of 315.72 and the following structural formula:



$C_{15}H_{10}ClN_3O_3$

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 1-4 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

Clonazepam tablets are 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 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 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 pediatric patients (see **INDICATIONS** and **DOSAGE AND ADMINISTRATION** sections).

ADVERSE REACTIONS
The most frequently occurring side effects of clonazepam are referable to CNS depression. Experience in treatment of seizures 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 with seizure disorders 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
Clonazepam tablets, USP are available as 0.5 mg tablets, light yellow, round, biconvex, imprinted *E* over 63 on one side and bisected on the other; 1 mg tablets, light blue, round, biconvex, imprinted *E* over 64 on one side and bisected on the other; 2 mg tablets, white, round, biconvex, imprinted *E* over 65 on one side and bisected on the other; in bottles of 100, 500, and 1000.

Store at controlled room temperature 15°-30°C (59°-86°F).

Dispense in tight, light-resistant containers as defined in the USP, with a child-resistant closure, as required.

CAUTION: Federal law prohibits dispensing without prescription.

Manufactured by:
Eon Labs Manufacturing, Inc.
Laurelton, NY 11413

Revised 07/97
MF0063REV0797
Flat #12628

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074979

CHEMISTRY REVIEW(S)

1. CHEMIST'S REVIEW NO. 2

2. ANDA ***74-979***

3. NAME AND ADDRESS OF APPLICANT
Eon Labs Manufacturing, Inc.
227-15 North Conduit Avenue
Laurelton, NY 11413

4. LEGAL BASIS FOR ANDA SUBMISSION
Generic version of Hoffmann-LaRoche's **KLONOPIN**® (NDA 17-533). Patent certification and exclusivity statement are provided (pp. 002-005).

5. SUPPLEMENT(s) N/A

6. ESTABLISHED NAME
Clonazepam Tablets

7. PROPRIETARY NAME
N/A

8. SUPPLEMENT(s) PROVIDE(s) FOR Original ANDA

9. AMENDMENTS AND OTHER DATES

Firm		**FDA**	
Orig. submission	10/7/96	ANDA acknowledgment letter	12/09/96
		CSO review	12/02/96
		Labeling review	1/29/97
		Bio review	
		Deficiency letter	03/04/97
Amendment (minor)	04/08/97		
Amendment (fax)	06/20/97		
Amendment (labeling)	07/14/97		
Amendment (fax)	08/25/97		
Amendment (fax)	08/27/97		

This review covers submissions dated 04/08 thru 08/27/97.

10. PHARMACOLOGICAL CATEGORY
Anticonvulsant - Used alone or as an adjunct in the treatment of the Lennox-Gastaut syndrom (petit mal variant), akinetic and myoclonic seizures.

11. Rx or OTC
℞

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM

Tablets (Oral)

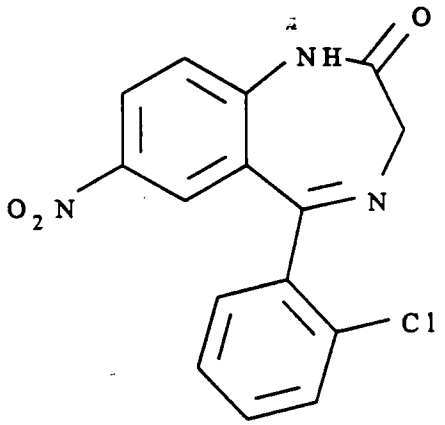
14. STRENGTH(S)

0.5 mg, 1.0 mg and 2.0 mg

15. CHEMICAL NAME AND STRUCTURE USP 23, page 373

Clonazepam USP

$C_{15}H_{10}ClN_3O_3$; M.W. = 315.72



5-(*o*-Chlorophenyl)-1,3-dihydro-7-nitro-
2*H*-1,4-benzodiazepin-2-one. CAS [1622-61-3]

Drug substance and drug product are official USP 23 items

16. RECORDS AND REPORTS None

17. COMMENTS

a. Application is suitable for approval.
b. Labeling found **satisfactory**, dated 5/9/97.
c. Bio found acceptable.
d. DMF found satisfactory, dated 1/31/97
e. Methods validation is not required, drug substance and drug product are compendia.
f. Established Inspection Request acceptable, dated 4/15/97.

18. CONCLUSIONS AND RECOMMENDATIONS

APPROVE

19. REVIEWER: Raymond Brown

DATE COMPLETED: August 28, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074979

BIOEQUIVALENCE REVIEW(S)

ANDA 74-979

Eon Labs Manufacturing, Inc.
Attention: Sadie M. Ciganek
227-15 North Conduit Avenue
Laruelton NY 11413

APR 14 1997

Dear Madam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Clonazepam Tablets USP, 0.5 mg, 1.0 mg and 2.0 mg.

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

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

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

for Nicholas Fleischer, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

APR 8 1997

Clonazepam
0.5, 1 and 2 mg Tablets
ANDA #74-979
Reviewer: Moheb H. Makary
WP 74979SDW.096

Eon Labs Manufacturing, Inc.
Laurelton, NY.
Submission Date:
October 7, 1996

Review of a Bioequivalence Study, Dissolution Testing and Waiver Requests

I. Objective:

Eon Labs Manufacturing, Inc., has submitted results of a comparative bioequivalence study and dissolution testing conducted on its test product, Clonazepam Tablet, 1 mg, and Klonopin® 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® 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 #960205 For Single-Dose, Two-Way Crossover

Bioavailability Study of Clonazepam 1 mg Tablet Under Fasting Conditions:

Study site:

Analytical site:

Sponsor:	Eon Labs Manufacturing, Inc. Laurelton, NY.
Investigators:	Medical Director Senior Director
Study design:	Single-dose, randomized, 2-way crossover study, under fasting conditions
Subjects:	Twenty-three (23) healthy adult male volunteers enrolled in this study. Subject #10 did not complete the crossover. In order to restore sufficient statistical power, 4 additional healthy males enrolled in and completed the study. Thus, a total of 26 subjects completed the crossover. Subject Nos. 1-25 (subjects originally assigned #9 and #12 withdrew prior to period I dosing) were dosed on June 22 and July 13, 1996, subject Nos. 26-29 were dosed on July 13 and August 3, 1996. Inadvertently, all 26 subjects that completed the study were analyzed for clonazepam in plasma. As per protocol, statistical and pharmacokinetic analyses were performed on data from 24 subjects (subject Nos. 1-8, 11, 13-26, 28).
Inclusion criteria:	The subjects were between 18 and 45 years old. They were within 15% 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 7 days prior to start the study.

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

Test product: A. 1X1 mg clonazepam, (Eon Labs Manufacturing, Inc.), lot # 960502, Exp. N/A. lot size Tablets, Content uniformity 97.9% (CV=0.9%), potency 97.0%.

Reference product: B. 1x1 mg Klonopin® Tablet (Roche Pharma Inc.), lot #2140, Exp. 8/97, content uniformity 100.4% (CV=2.0%), potency 96.2%.

Food and fluid intake: Single, oral 1 mg (1 tablet) dose administered with 240 mL of water. Meals were provided at 4 and 9 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 -22°C pending assay.

Washout period: Three weeks

Assay methodology:

Specificity:

Recovery:

Sensitivity:

Linearty:

Precision:

Stability:

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 LNCmax.

IV. In Vivo Results:

Twenty-three healthy male volunteers enrolled in the study (June 22, 1996), one subject did not completed the crossover. Subject #10 withdrew from the study prior to period 2 dosing for personal reasons; he did not return for period 2. Thus, a total of 22 subject completed the study. An additional group of 4 subjects (subject Nos. 26-29)enrolled in and completed the study (July 13, 1996). Therefore, a total of 26 subjects completed the crossover. Subjects #3 experienced an infected spider bite on his right calf 14.5 days after period 1 dosing. Subject #24 experienced a mild cough 1.6 days after period 2 dosing. Subject #25 experienced a mild headache 2.3 days after period 1 dosing and vomiting 4.9 days after period 1 dosing. These events were mild in intensity and were resolved.

As per protocol, statistical and pharmacokinetic analyses were performed on data from 24 subjects (subjects Nos. 1-8, 11, 13-26, 28).

The plasma concentrations and pharmacokinetic parameters are summarized in Table I.

Table I

Mean Plasma Concentrations And Pharmacokinetic Parameters
Following An Oral Dose of 1 mg (1mg Tablet)
Clonazepam Under Fasting Conditions
(N=24)

Time (hr)	Eon Labs Test product Lot #960502 ng/mL (C.V.)	Roche Pharma Reference product Lot #2140 ng/mL (C.V.)
0	0.00	0.00
0.25	0.01 (489.9)	0.02 (372.8)
0.50	1.01 (95.1)	0.68 (81.9)
0.75	3.04 (58.3)	2.22 (54.1)
1	4.28 (42.7)	3.78 (45.5)
1.50	5.10 (33.8)	5.28 (29.5)
2.00	5.22 (26.8)	5.75 (23.3)
2.50	5.78 (20.1)	5.84 (20.8)
3	5.46 (17.7)	5.92 (19.5)
3.5	5.42 (18.0)	5.66 (15.2)
4	5.90 (18.8)	6.26 (16.4)
6.0	4.57 (18.0)	4.75 (17.5)
8	4.12 (18.8)	4.38 (19.6)
12	3.76 (19.8)	4.11 (20.0)
24	2.72 (22.6)	3.01 (21.1)
36	2.35 (19.2)	2.36 (18.5)
48	1.62 (18.5)	1.85 (19.8)
72	1.17 (20.4)	1.27 (24.1)
96	0.73 (22.2)	0.81 (19.5)

120	0.49 (22.8)	0.52 (23.8)
144	0.31 (31.0)	0.33 (31.4)
168	0.20 (29.6)	0.23 (33.9)

	Test	Reference	90% CI
AUC(0-t) (ng.hr/mL)	232.1(15.8)	250.5(15.7)	
AUCinf (ng.hr/mL)	243.4(15.9)	263.8(15.4)	
CMAX (ng/mL)	6.4(19.8)	6.6(17.8)	
TMAX (hr)	2.96	3.15	
Kel (1/hr)	0.02	0.02	
Half-life (hr)	38.53	38.82	
LNAUC(0-t)			90.1-95.1%
LNAUCinf			89.7-95.1%
LNCMAX			90.0-104.0%

1. Eon's test product had an AUC(0-t) of 232.1 ng.hr/mL, AUCinf of 243.4 ng.hr/mL and Cmax of 6.4 ng/mL, which were 7.3%, 7.7% and 3.0% lower, respectively, than their reference product values. The differences were statistically significant for AUC(0-t) and AUCinf. The 90% confidence intervals were within the acceptable range of 80-125% for log-transformed AUC(0-t), AUCinf. And Cmax.

2. Clonazepam plasma levels peaked at 4 hours for both the test and reference products following their administration under fasting conditions.

3. It should be noted that after including in the statistical analysis of all subjects who completed the study (26 subjects), the resulting 90% confidence intervals for clonazepam remained the same as shown below:

LNAUC(0-t)	90.2-95.2%
LNAUCinf	89.7-94.9%
LNCMAX	90.6-104.2%

All confidence intervals remained within the acceptable 80-125% range.

V. Formulations:

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

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:	Eon's Clonazepam 0.5 mg Tablets, lot #960504 1 mg Tablets, lot #960502 2 mg Tablets, lot #960503
Reference Products:	Roche's Klonopin^{R} 0.5 mg Tablets, lot #1849 1 mg Tablets, lot #2140 2 mg Tablets, lot #3047
Specifications:	NLT in 60 minutes

Dissolution testing results are shown in Table III.

VII. Comments:

1. The confidence intervals for LNAUC(0-t), LNAUCinf and LNCmax are within the acceptable range of 80-125% 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 Eon Labs Manufacturing, Inc., on its Clonazepam 1 mg Tablet, lot #960502, comparing it to Klonopin^{R} 1 mg Tablet manufactured by Roche Pharma, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Eon'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 Eon Labs Manufacturing Inc., on its Clonazepam 0.5 mg Tablets, lot #960504, 1 mg lot #960502 and 2 mg Tablets, lot #960503, 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 Eon Labs Manufacturing 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

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

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE Date: 4/4/97

Concur: Date: 4/8/97
Nicholas Fleischer, Ph.D.
Director
Division of Bioequivalence

MMakary/4-2-97 wp 74979SDW.096
cc: ANDA #74-979, original, HFD-658 (Makary), Drug File, Division File.

Table III. In Vitro Dissolution Testing

Drug (Generic Name):Clonazepam
Dose Strength: 0.5 mg, 1 mg and 2 mg
ANDA No.: 74-979
Firm: Eon
Submission Date: October 7, 1996
File Name: 74979SDW.O96

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 # 960504 Strength(mg) 0.5			Reference Product Lot # 1849 Strength(mg) 0.5		
	Mean %	Range	%CV	Mean %	Range	%CV
5	63.1		13.1	26.6		10.0
15	90.1		2.5	80.4		1.8
30	94.9		1.6	94.6		1.3
60	98.2		1.4	101.0		1.2
75	99.5		1.5	103.2		1.2

Sampling Times (Minutes)	Test Product Lot # 960502 Strength(mg) 1			Reference Product Lot # 2140 Strength(mg) 1		
	Mean %	Range	%CV	Mean %	Range	%CV
5	40.8		14.9	28.6		7.7
15	85.2		0.9	81.4		3.3
30	91.8		1.0	94.0		1.2
60	95.4		1.0	100.3		1.3
75	97.2		1.1	100.9		1.0

Sampling Times (Minutes)	Test Product Lot # 960503 Strength(mg) 2			Reference Product Lot # 3047 Strength(mg) 2		
	Mean %	Range	%CV	Mean %	Range	%CV
5	48.8		12.0	22.6		7.4
15	83.9		5.3	75.0		1.9
30	90.8		2.1	92.2		0.9
60	94.1		0.8	100.6		1.1
75	95.3		0.7	100.2		0.6

COMPARISON OF COMPOSITIONS FOR CLONAZEPAM TABLETS, USP 0.5 MG, 1.0 MG, AND 2.0 MG

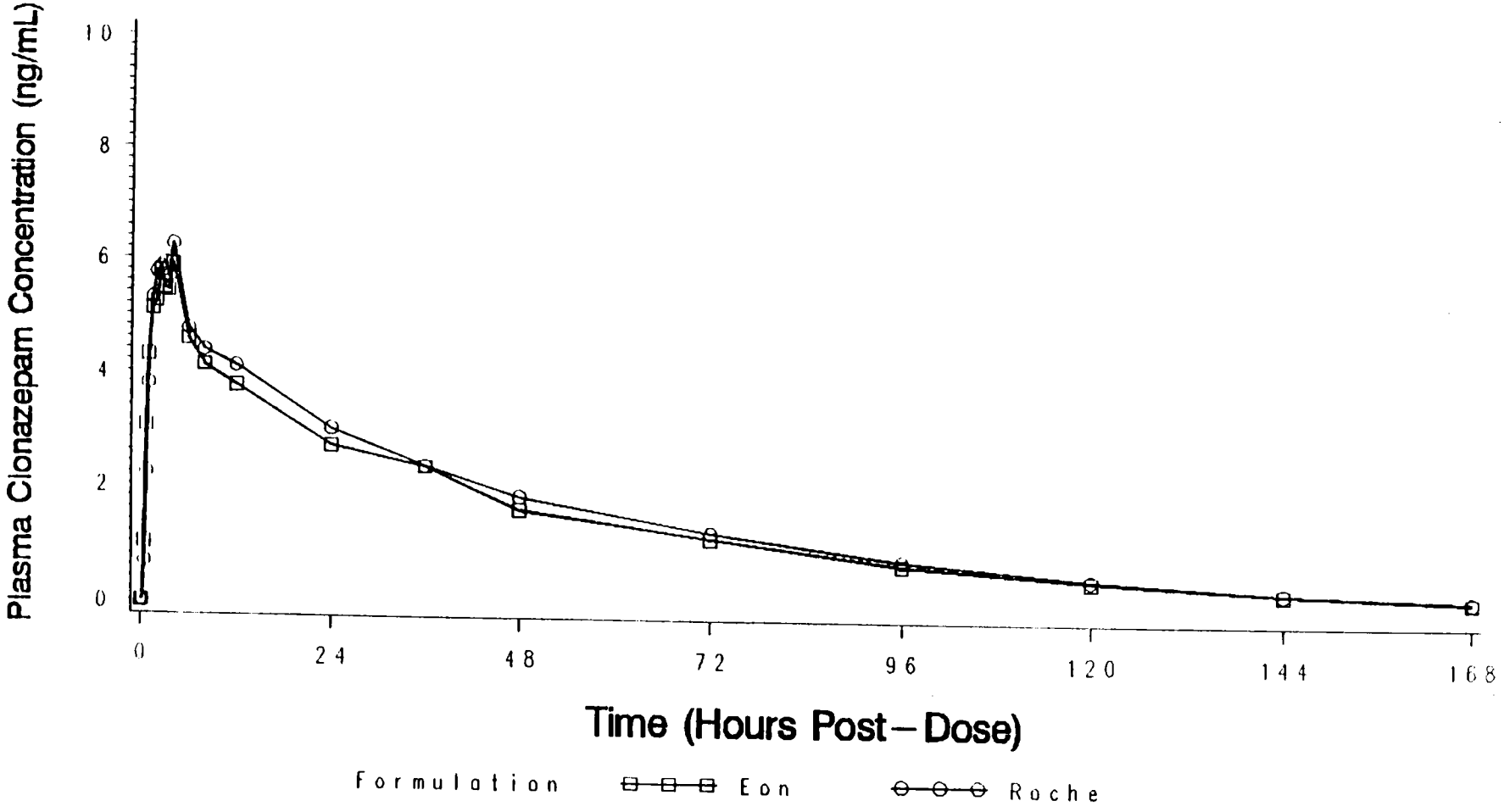
Component	Clonazepam 0.5 mg Tablets		Clonazepam 1.0 mg Tablets		Clonazepam 2.0 mg Tablets	
	Amount per Tablet (mg)	% w/w	Amount per Tablet (mg)	% w/w	Amount per Tablet (mg)	% w/w
Clonazepam, USP	0.5	0.29	1.0	0.59	2.0	1.18
Lactose Anhydrous, NF						
Microcrystalline Cellulose, NF						
Corn Starch, NF						
Magnesium Stearate, NF						
D&C Yellow # 10						
FD&C Blue # 1						
TOTALS	170.0	100.00	170.0	100.00	170.0	100.00

Figure 2

Project No. 960205

Mean Plasma Clonazepam Concentrations

(Linear Plot)



[redacted]

Table D5
Project Number :960205
Clonazepam in Plasma
Ratio Analysis - AUC 0-t (ng·h/mL)

Subject	(A)	(B)	(A/B)%
1			
2			
3			
4			
5			
6			
7			
8			
11			
13			
14			
15			
16			
17			
18			
19			
20			
21			
22			
23			
24			
25			
26			
28			
Arithmetic Mean	232.1	250.5	93.01
± SD	36.67	39.34	7.284
CV%	15.8	15.7	7.8
n	24	24	24

Eon (A) vs Roche (B)

PhAST RTAB 2.3-000

DEFAULT

Table D6
Project Number :960205
Clonazepam in Plasma
Ratio Analysis - AUCinf (ng·h/mL)

Subject	(A)	(B)	(A/B)%
1			
2			
3			
4			
5			
6			
7			
8			
11			
13			
14			
15			
16			
17			
18			
19			
20			
21			
22			
23			
24			
25			
26			
28			
Arithmetic Mean	243.4	263.8	92.64
± SD	38.67	40.50	7.549
CV%	15.9	15.4	8.1
n	24	24	24

Eon (A) vs Roche (B)

PhAST RTAB 2.3-000

DEFAULT

Table D7
Project Number :960205
Clonazepam in Plasma
Ratio Analysis - Cmax (ng/mL)

Subject	(A)	(B)	(A/B)%
1			
2			
3			
4			
5			
6			
7			
8			
11			
13			
14			
15			
16			
17			
18			
19			
20			
21			
22			
23			
24			
25			
26			
28			
Arithmetic Mean	6.4151	6.6165	98.76
± SD	1.26925	1.17648	21.534
CV%	19.8	17.8	21.8
n	24	24	24

Eon (A) vs Roche (B)

PhAST RTAB 2.3-000 DEFAULT