CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074925

Trade Name : CLONAZEPAM TABLETS USP

Generic Name: Clonazepam Tablets USP, 0.5mg, 1mg and 2mg

Sponsor : Invamed, Inc.

Approval Date: September 30, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074925

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074925

APPROVAL LETTER

ANDA 74-925

SEP 30 1997

Invamed Inc.
Attention: Mahendra R. Patel
2400 Route 130
Dayton, NJ 08810

Dear Sir:

This is in reference to your abbreviated new drug application dated July 12, 1996, 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 December 24, 1996, July 1 and 18, 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 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. 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,

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074925

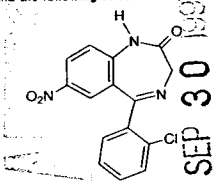
FINAL PRINTED LABELING

0 119835 5

CLONAZEPAM TABLETS USP C IV

DESCRIPTION

Clonazepam, a benzodiazepine is chemically known as 5-(*o*-Chlorophenyl)-1,3-dihydro-7-nitro-2H-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 having a molecular formula $C_{15}H_{10}ClN_3O_3$ and the following structural formula:



Clonazepam tablets, for oral administration, contain 0.5 mg, 1 mg or 2 mg clonazepam. In addition, each tablet contains the following inactive ingredients: corn starch, lactose monohydrate, magnesium stearate and microcrystalline cellulose. Clonazepam Tablets USP, 0.5 mg contain D&C Yellow No. 10 Aluminum Lake while Clonazepam Tablets USP, 1 mg contain D&C Yellow No. 10 Aluminum Lake and FD&C Blue No. 1 Aluminum Lake as colorant.

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

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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 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 three 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, 1.0, 5.0, or 10.0 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

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 func-

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 judgement, 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 ADMINISTRATIONS 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, rhi-

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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

dence

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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, 0.5 mg are yellow, round, uncoated, engraved INV above the bisect and 353 below the bisect on one side are supplied as follows:

NDC 52189-353-24 in bottles of 100 tablets

NDC 52189-353-30 in bottles of 1000 tablets

Clonazepam Tablets USP, 1 mg are green, round, uncoated, engraved INV

tablets

Clonazepam Tablets USP, 2 mg are white, round, uncoated, engraved INV above the bisect and 355 below the bisect on one side are supplied as follows:

NDC 52189-355-24 in bottles of 100 tablets

NDC 52189-355-30 in bottles of 1000 tablets

Store at 15°C to 30°C (59°F to 86°F).

Dispense in a tight, light-resistant container as defined in USP.

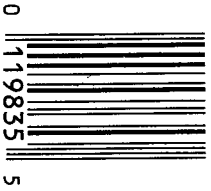
Caution

Federal law prohibits dispensing without prescription.

Manufactured by:
INVAMED, INC.
Dayton, NJ 08810 USA

Date of Revision: July 1997
L-1198; MF #1095C

8



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074925

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 3

2. ANDA # 74-925

3. NAME AND ADDRESS OF APPLICANT
Invamed Inc.
Attention: Mahendra Patel
2400 Rt. 130
Dayton, NY 08810

4. BASIS OF SUBMISSION
The applicant certifies that to the best of their knowledge there are no unexpired patents or exclusivities for Clonazepam Tablets USP, 0.5 mg, 1 mg and 2 mg.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME

7. NONPROPRIETARY NAME
Clonazepam

8. SUPPLEMENT PROVIDE FOR:
N/A

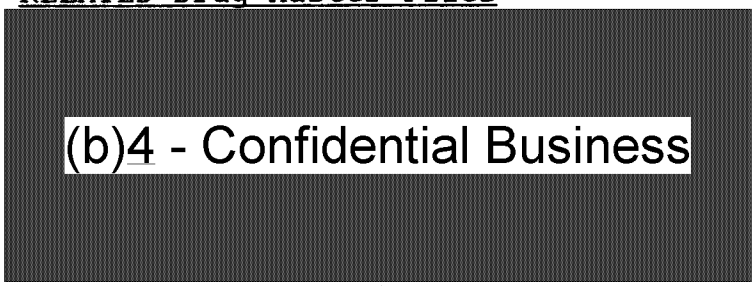
9. AMENDMENTS AND OTHER DATES:

July 12, 1996--	Original Submission
December 3, 1996--	Deficiency letter
December 24, 1996--	Amendment
February 11, 1997--	New Correspondence
April 4, 1997--	Labeling review
June 24, 1997--	Deficiency letter
July 1, 1997--	Amendment
July 11, 1997--	Telecom--Labeling
July 18, 1997--	Telecom Amendment

10. PHARMACOLOGICAL CATEGORY
Anticonvulsant

11. Rx or OTC
Rx

12. RELATED Drug Master Files



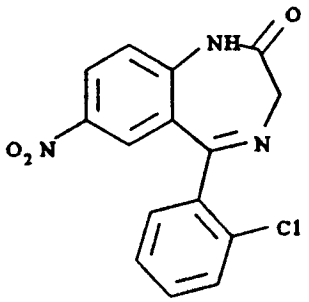
13. DOSAGE FORM
Tablets

14. POTENCY
0.5 mg, 1 mg & 2 mg

15. CHEMICAL NAME AND STRUCTURE

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]

16. RECORDS AND REPORTS

N/A

17. COMMENTS

None.

18. CONCLUSIONS AND RECOMMENDATIONS

Recommend approval letter to issue.

19. REVIEWER: Edwin Ramos

DATE COMPLETED: July 8, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

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BIOEQUIVALENCE REVIEW(S)

ANDA 74-925

Invamed Inc.
Attention: Mahendra R. Patel, Ph.D.
2400 Route 130
Dayton NJ 08810

JAN - 6 1997

Dear Sir:

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 mg, and 2 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,

/S/

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

JAN 6 1997

Clonazepam Tablets, 0.5 mg, 1 mg and 2 mg
ANDA # 74-925
Reviewer: Man M. Kochhar
74925SWD.796

Invamed Inc.
Dayton, New Jersey
Submission Date:
July 13, 1996

Review of a Bioequivalence Study, a Waiver Request and Dissolution

I. BACKGROUND

Clonazepam is a benzodiazepine with a pharmacological profile similar to other anxiolytic/sedative benzodiazepines. It is indicated for the management of myoclonic or akinetic seizures and Lannox-Gastaut syndrome.

Clonazepam is 98% absorbed and extensively metabolized with a half-life of about 18-50 hours. Less than 1% of an oral dose is excreted in the urine. The drug is 86% plasma protein bound.

The innovator product [Klonopin Tablets (Roche)] is available in 3 strengths - 0.5, 1 and 2 mg. Due to side effects (drowsiness, ataxia, personality changes, etc.), the recommended adult dose is 1.5 mg daily in 3 divided doses. Doses may be increased by 0.5 - 1 mg every 3 days until seizures are controlled.

II. OBJECTIVE

The objective of this study is to determine whether Invamed's 1.0 mg clonazepam tablets are bioequivalent to Roche (Klonopin) clonazepam tablets under single dose fasting conditions. The firm is requesting a waiver for 0.5 mg and 2.0 mg tablet based on an acceptable 1 mg bioequivalence study under fasting conditions.

III. IN-VIVO STUDY

The Purpose of this study is to assess the bioequivalence of two formulations of clonazepam 1 mg tablet by Invamed, compared with Klonopin 1 mg tablet by Roche when given under fasting conditions.

The bioequivalence study was conducted at [redacted] (b)4 Confidential Business [redacted]

IV. STUDY DESIGN

The study was designed as a randomized, single dose, two-way crossover bioequivalence study in 32 healthy volunteers under

fasting conditions.

Number of Subjects: 32 healthy male volunteers were enrolled in the study. 31 subjects completed the study. Subject #8 did not show up for phase 2.

Treatments: A. Test: 1 x 1 mg tablet (Invamed clonazepam lot # D960202) with 240 mL of water.

Batch Size: (b)4 - Expiration Date: n/a
Potency:97.0 %; Content Uniformity:100.9 %

B. Reference: 1 x1 mg tablet Klonopin, (Roche lot # 2139) with 240 mL of water.

Expiry: 8/97; Potency:98.3%
Content Uniformity: 101.1%

Blood Samples: Samples were collected in Vacutainers containing EDTA before dosing (10 mL) and at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 16, 24, 36,48, 72, 96, 120, and 144 hours after dosing.

Fasting/Meals: Fast for 10 hours before dosing and 4 hours after dosing. Meals or snacks were served at 4 hours after dosing, and at appropriate times thereafter; meal plans identical for both periods. Water was permitted ad lib. until 1 hour before dosing and one hour after dosing.

Housing: From 10 hours before dosing until after the collection of 48 hours blood sample. Subjects returned to the facility for the subsequent 4 blood drawings.

Washout Period: 21 days between doses.

Analytical Method: (b)4 - Confidential Business

Subject Screening:

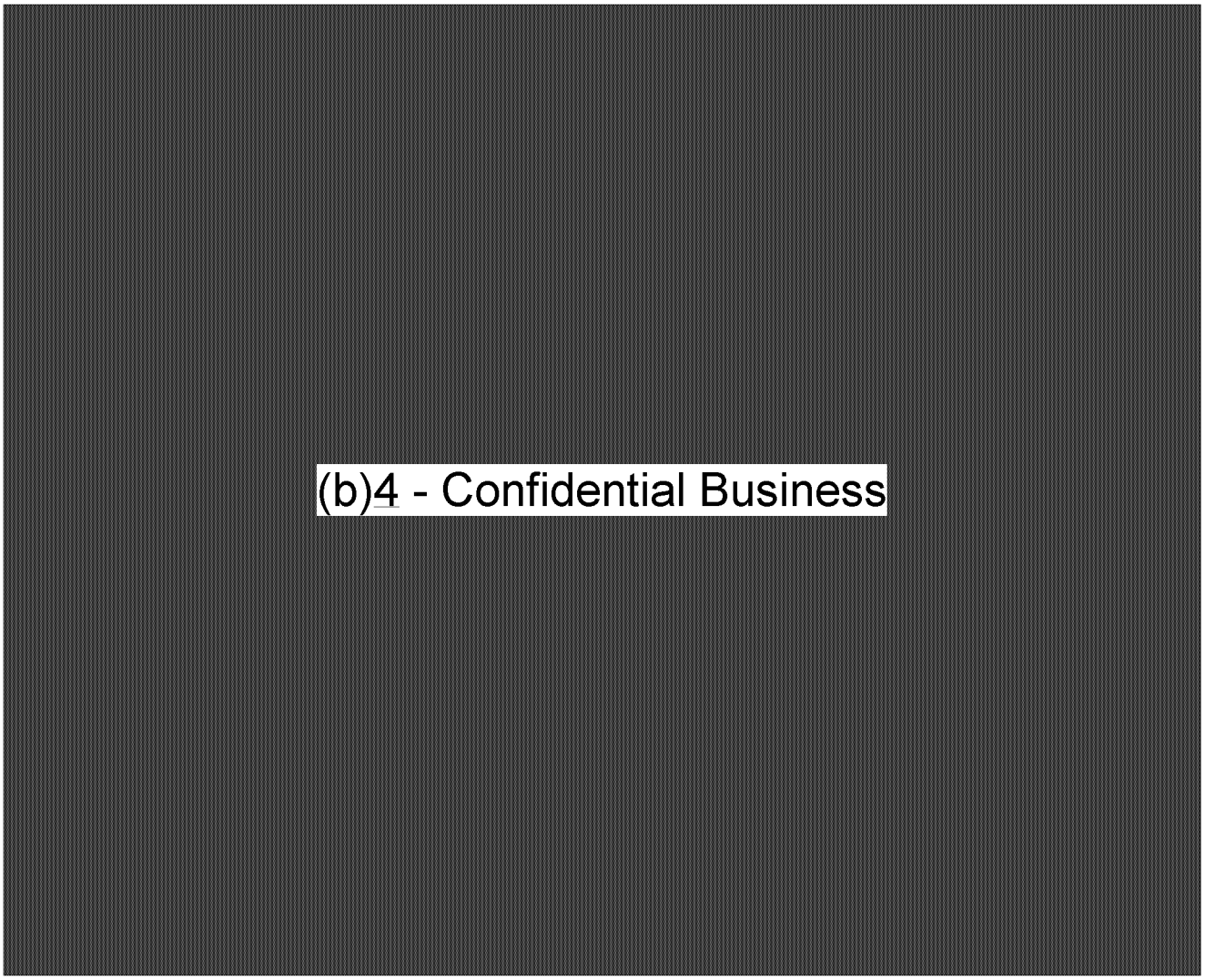
In this study volunteers were selected between the ages of 18-40, and within ±15% of their frame and size according to Metropolitan Life Insurance Company Bulletin,1983. The subjects were selected for this study after i) physical examination, ii) medical and complete laboratory tests (blood chemistry, hematology, urinalysis, etc.). The volunteers were instructed not to take any prescription medications and/or OTC preparations for at least one week prior to the start and until the end of the

study. The volunteers were not allowed to drink alcoholic beverages or caffeine-containing products for 48 hours prior to dosing and during the periods when blood samples being collected. Each subject signed a written informed consent form.

Pharmacokinetic and Statistical Analysis:

Plasma concentration-time profiles of clonazepam were analyzed pharmacokinetically and statistically to evaluate relative bioavailability of test product to reference product. Significance of differences due to treatments, phase, dosing and sequence were evaluated for plasma clonazepam concentrations at each sampling time and Cmax, Tmax, Kel, t1/2 and AUC by ANOVA using SAS (GLM procedure).The power to detect 20% differences between formulations (t-test method), and 90% confidence intervals (two,one-sided t-test method) were calculated for each major pharmacokinetic parameter.

ASSAY VALIDATION



(b)4 - Confidential Business

DATA ANALYSIS:

Individual analysis of variance (ANOVA with factors including drug, phase, sequence and subjects within sequence) were carried out to compare formulations at each sampling time, AUC (0-t), AUC (inf.), Cmax, Tmax, t1/2 and Kel. All ANOVAs were performed with SAS General Linear Models Procedures (GLM). 90% confidence intervals (two one-sided t-test method) were calculated for clonazepam pharmacokinetic parameters. For all analyses, effects were considered statistically significant if the probability associated with 'F' was less than 0.05.

IN VIVO BIOEQUIVALENCE STUDY RESULTS:

Of the 32 subjects enrolled in the study, 31 completed the crossover. Subject # 8 did not show up for Phase 2.The plasma samples from 31 subjects were assayed for clonazepam as per the protocol. The study was completed with no major protocol violations. The results of the study comparing the bioavailability of clonazepam are given in Table 1 and 2. The mean plasma clonazepam concentrations are given in Figure 1.

TABLE 1

Mean Plasma Concentration of Clonazepam (N=31)

Time (hours)	Invamed's Clonazepam Lot # D960202 ng/mL (CV%)	Roche's Klonopin Lot # 2139 ng/mL (CV%)	T/R
0	0 (-)	0 (-)	0.0
0.50	1.99 (80)	0.67 (72)	2.97
0.75	3.91 (46)	2.36 (49)	1.65
1	5.08 (34)	3.84 (39)	1.32
1.50	5.35 (26)	4.75 (32)	1.12
2	5.42 (22)	5.23 (25)	1.03
2.5	5.42 (19)	5.31 (22)	1.02
3	5.36 (18)	5.24 (19)	1.02
3.5	5.17 (17)	5.18 (17)	0.99
4	5.14 (16)	5.18 (17)	0.99
6	4.46 (17)	4.49 (16)	0.99
8	4.07 (18)	4.19 (15)	0.97
12	3.68 (18)	3.73 (16)	0.98
16	3.29 (17)	3.32 (17)	0.99
24	2.81 (17)	2.86 (17)	0.98
36	2.25 (18)	2.25 (17)	1.00
48	1.78 (18)	1.78 (16)	1.00
72	1.16 (22)	1.17 (20)	0.99
96	0.77 (26)	0.78 (24)	0.99
120	0.49 (28)	0.49 (30)	1.00
144	0.30 (59)	0.30 (59)	1.00

Table 2

A Summary of Clonazepam Pharmacokinetic Parameters for 31 subjects

Parameters	Invamed's Clonazepam	Roche's Klonopin	T/R	90% Confidence Interval
AUC_{0-144} ng.hr/mL	227.24 (18)	227.02 (16)	1.00	98; 102
AUC_{0-inf} ng.hr/mL	249.04 (18)	248.45 (17)	1.00	97; 103
C_{max} ng/mL	6.06 (20)	5.78 (18)	1.05	101; 107
T_{max} (hours)	2.01 (44)	2.71 (42)	0.74	

$t_{1/2}$ (hours)	39.55 (14)	39.19 (15)	1.01	
K_{el} (1/hour)	0.018 (14)	0.018 (14)	1.00	
Ln AUC_{0-144} ng.hr/mL	5.41 (3)	5.41 (3)	1.00	97; 102
Ln AUC_{inf} ng.hr/mL	5.50 (3)	5.50 (3)	1.00	97; 103
Ln C_{max} ng/mL	1.78 (11)	1.74 (10)	1.02	100; 109

The clonazepam AUC_{0-t} and AUC_{0-inf} produced by Invamed's formulation were 0.01% higher and 0.23% higher respectively than the values for the reference drug. The C_{max} was 4.8% higher than the reference. T_{max} was 25.8% lower for the test drug. $t_{1/2}$ and K_{el} values differ only by less than 1%. ANOVA performed on the plasma clonazepam concentration data at each of the twenty one sampling times detected statistically significant differences at 0.5, 0.75 and 1 hour between the two formulations. The firm did calculate Ln AUC and Ln Cmax for clonazepam and the 90% confidence intervals for log-transformed parameters were 97 to 102 for Ln AUC0-t, 97 to 103 for Ln AUCinf, and 100 to 109 for Ln Cmax.

The 90% confidence interval for clonazepam for AUC_{0-144} and AUC_{0-inf} and C_{max} were well within ±20% limits set for defining product bioequivalence, in a fasting study.

The central nervous system (CNS) depressant effect of clonazepam was observed in 28 subjects. There were minor adverse events reported; dysnpea (1), weakness (1), headache (4), dry mouth (1), pain (1), pharyngitis (7), purpura (1), respiratory disorder (1), rhinitis (5); dizziness (2). There were no serious adverse effects which required dropping any subjects from the study or required therapeutic medical intervention.

On the basis of fasting in vivo bioavailability data it is determined that Invamed's clonazepam 1 mg tablets and Roche's Klonopin 1 mg tablets are bioequivalent under fasting conditions.

DISSOLUTION TEST RESULTS:

In vitro dissolution testing was conducted in 900 mL of water at 37°C using USP XXIII apparatus 2 (paddle) at 100 rpm. Results are presented in Table 3. Both the test and reference products meet the dissolution specifications of not less than [(b)4] of the labeled amount of drug dissolved from the tablets in 60 minutes.

COMMENTS:

1. The study was conducted in 31 healthy volunteers comparing the plasma concentrations from Invamed's clonazepam 1 mg tablets to that of reference Klonopin 1 mg tablets manufactured by Roche. The clonazepam AUC_{0-144}, AUC_{0-inf}, C_{max} of the Invamed formulation were 0.01% higher, 0.23% higher, and 4.8% higher respectively than the corresponding Roche's reference values. ANOVA performed on the plasma clonazepam concentration data detected statistically significant differences at 0.5, .75 and 1 hour between two formulations. These results indicate that the test drug is bioequivalent to the reference product under fasting conditions.

2. Analysis of variance indicated no statistical significant treatment differences or group-by-sequence effect for AUC and Cmax for clonazepam. The 90% confidence intervals were well within the limits of ±20%.

3. The validation studies conducted by the sponsor for clonazepam are acceptable to the Division of Bioequivalence.

4. The firm is requesting a waiver for 0.5 mg, and 2.0 mg clonazepam tablets based on the fasting bioequivalence study on 1 mg tablet. Therefore, the waiver for 0.5 mg and 2 mg tablet is granted based on an acceptable fasting study on 1 mg tablet.

5 The in vitro dissolution testing conducted for 1 mg tablets of the test and reference products shows greater than [illegible]f the labeled amount of the clonazepam dissolved in 60 minutes.

6. The lots of test and reference products employed in the in vitro dissolution test were identical to those employed in the in vivo bioequivalence study.

7. The in vivo fasting bioequivalence study is acceptable.

8. The firm has demonstrated that the formulations of its clonazepam tablets, 0.5 mg, 1.0 mg, and 2.0 mg are proportional with respect to active and inactive ingredients (Table 4).

DEFICIENCY: None

RECOMMENDATIONS:

1. The fasting bioequivalence study conducted by Invamed on its Clonazepam 1 mg tablets, lot # D960202, comparing it to Klonopin 1 mg tablets, lot # 2139 manufactured by Roche Inc. has been found acceptable by the Division of Bioequivalence. The study demonstrates that under fasting conditions the Invamed's Clonazepam 1 mg tablets are bioequivalent to the reference product, Klonopin 1 mg tablets manufactured by Roche.

2. The formulations for 0.5 mg, and 2.0 mg Clonazepam tablets are proportionally similar to 1 mg Clonazepam tablet which underwent bioequivalence study. The waiver of in vivo bioequivalence study requirement for Invamed 0.5 mg and 2.0 mg tablets is granted. The 0.5 mg and 2.0 mg Clonazepam tablets from Invamed are therefore, deemed bioequivalent to 0.5 mg, and 2.0 mg Klonopin tablets manufactured by Roche based on 21 CFR 320.22 (d)(2).

3. The in vitro test results are acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability programs.The dissolution testing should be conducted in 900 mL of water at 37°C using USP XXIII apparatus 2 (Paddle) at 100 rpm. The test product should meet the following specifications:

> Not less than (b)4 of the labeled amount of the drug in the tablet is dissolved in 60 minutes.

4. From the bioequivalence point of view, the firm has met the requirements for in vivo bioequivalence and in vitro dissolution test, and therefore, the application is acceptable.

The firm should be informed of the recommendations.

/S/

Man M.Kochhar, Ph.D.
Review Branch III
Division of Bioequivalence

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE

/S/ 12/12/96

Ramakant M. Mhatre, Ph.D
Branch Chief,
Review Branch III

/S/

Concur: _____ Date: 12/24/96

Rabindra Patnaik, Ph.D
Acting Director
Division of Bioequivalence

MMKochhar/mmk/10-23-96; 12-9-96; 74-925

cc: 74-925 original, HFD-600 (Hare), HFD-344 (CViswanathan), HFD-658 (Mhatre, Kochhar), Drug File, Division File

TABLE 3

DISSOLUTION

Drug: Clonazepam
ANDA # 74-925
Firm: Invamed
Submission Date: July 13, 1996

Conditions for Dissolution:

USP XXIII, Apparatus 2 (Paddle) at 100 rpm
No. of Units: 12
Medium: 900 mL of degassed water
Specifications: NLT (b)(4) in 60 minutes
Reference Drug: Klonopin by Roche

Results:

Sampling Times Minutes	**Clonazepam Lot # D960202 Strength 1 mg**			**Klonopin Lot # 2139 Strength 1 mg**		
	Mean%	**Range**	**RSD**	**Mean%**	**Range**	**RSD**
15	95.1	(b)(4) -	1.1%	96.3	(b)(4) -	4.1%
30	96.0		0.9%	97.5		2.3%
45	96.5		0.7%	99.8		2.1%
60	96.8		0.7%	100.1		1.1%

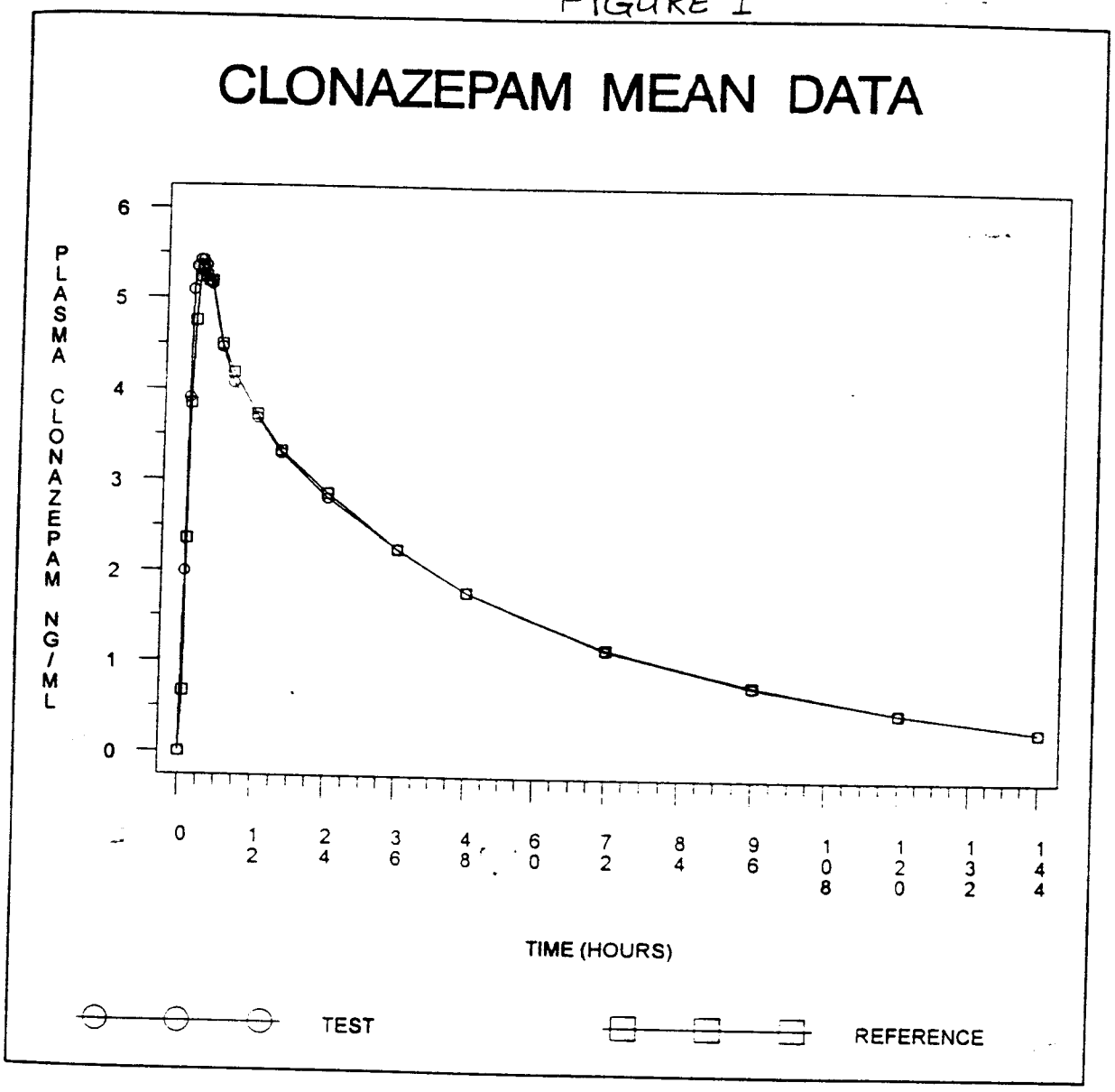
		Lot # 960302 Strength 0.5 mg			Lot # 1795 Strength 0.5 mg	
15	97.1	(b)(4) -	0.6%	99.2	(b)(4) -	2.2%
30	97.7		0.6%	100.4		2.4%
45	97.8		0.7%	99.2		2.5%
60	98.0		1.0%	97.1		4.2%

		Lot # 960301 Strength 2.0 mg			Lot # 3037 Strength 2.0 mg	
15	95.9	(b)(4) -	1.1%	92.1	(b)(4) -	3.0%
30	97.3		0.9%	96.2		1.0%
45	97.9		0.8%	97.9		1.1%
60	98.0		0.9%	98.5		0.9%

TABLE 4

Ingredients	**0,5 mg Tablet**	**1.0 mg Tablet**	**2.0 mg Tablet**
Clonazepam USP	0.5 mg	1.0 mg	2.0 mg
Microcrystalline Cellulose NF	(b)4 - Confidential Business		
Lactose Monohydrate NF			
Starch NF			
Magnesium Stearate NF			
Purified Water, USP			
D&C Yellow # 10			
D&C Blue # 1			
TOTAL TABLET WEIGHT	160.0 mg	160.0 mg	160.0 mg

FIGURE 1


CLONAZEPAM MEAN DATA
PLASMA CLONAZEPAM NG/ML
0
1
2
3
4
5
6
0
12
24
36
48
60
72
84
96
108
120
132
144
TIME (HOURS)
TEST
REFERENCE