On

ANDA 74-826

JUL 3 1997

Zenith Goldline Pharmaceuticals, Inc.
Attention: Karen Rocco
140 Legrand Avenue
Northvale, NJ 07647

Dear Madam:

This is in reference to your abbreviated new drug application dated December 29, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Estazolam Tablets, 1 mg and 2 mg.

Reference is also made to your amendments dated December 24, 1996, and June 5, 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 Estazolam Tablets, 1 mg and 2 mg, to be bioequivalent, and therefore therapeutically equivalent to the listed drug (Prosom® Tablets, 1 mg and 2 mg, respectively, of Abbott Laboratories, Pharmaceutical Products Division). 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,

Roger L. Williams, M.D.
Deputy Center Director for Pharmaceutical Science
Center for Drug Evaluation and Research

D, J

1. CHEMISTRY REVIEW NO 3

2. ANDA 74-826

3. NAME AND ADDRESS OF APPLICANT

Zenith Goldline Pharmaceuticals, Inc.
Northvale, NJ 07647

4. LEGAL BASIS FOR SUBMISSION

505(j) Prosom (Estazolam) Tablets, 1 mg & 2 mg
Abbott Laboratories, Inc.

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Estazolam Tablets

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

N/A

9. AMENDMENTS AND OTHER DATES:

DOA 12/29/95; Amend 2/12/96; NC 3/11/96; NC 3/22/96; Bio review & letter 5/23/96; NA & Chem review 6/24/96; Amend (Major) 12/23/96; Label rev 1/24/97; NA Fax 5/16/97. Fax Amend 6/5/97.

10. PHARMACOLOGICAL CATEGORY

Hypnotic

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM

White, square, flat-faced, beveled-edged, scored tablets, debossed "Z" above the bisect, "1" below the bisect, and "4036" on the other.

14. POTENCY

1 mg

Salmon colored, square, flat-faced, beveled-edged, scored tablets, debossed "Z" above the bisect, "2" below the bisect, and "4037" on the other. 2 mg

15. CHEMICAL NAME AND STRUCTURE

Satisfactory - See review #1.

16. RECORDS AND REPORTS

N/A

17. COMMENTS

DMF was found adequate on 5/7/97.

Bio review was completed on 5/26/96. The data was found acceptable. Bio accepted Zenith's Q value for their dissolution test of NLT in 30 minutes. This is different than the innovator's Q value, which is NLT in 45 minutes.

EER was found acceptable on 1/10/97. However Zenith was told by they were also approved for testing of exipients, in addition to testing of packaging materials.

We should verify this by submitting a follow-up EER to compliance.

Methods were satisfactorily validated by BLT-DO on 10/4/96. Response by Zenith to BLT-DO's concerns were satisfactorily addressed.

Chemistry now satisfactory.

18. CONCLUSIONS AND RECOMMENDATIONS

Approve ANDA 74-826 pending verification of US Testing's true testing status.

19. REVIEWER: DATE COMPLETED:

Stephen Sherken June 12, 1997

ANDA Number: 74-826

FIRM: Zenith Goldline Pharmaceuticals, Inc.

DOSAGE FORM: Tablets

STRENGTH 1 mg and 2 mg tablets.

CGMP STATEMENT/EER UPDATE STATEMENT:

EER found acceptable on 1/10/97. Need follow-up EER since Zenith wants to use for the testing of packaging material and excipients. Compliance indicated in the EER that should only be used for the testing of packaging materials.

BIO STUDY: Bio study found acceptable on 5/26/96.

METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM)

Methods for Estazolam Bulk and Estazolam Tablets were satisfactorily validated, with comments by the BLT-DO laboratory, on 10/4/96. The response by Zenith to BLT-DO Laboratory's concerns were satisfactory. Methods were validated on Zenith's 1 mg tablets. The description of the dosage form is the same as the firms description found in Zenith's labeling.

STABILITY - ARE THE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION

Three month stability data at 40°C/75% RH for the 1 mg tablet (lot MD-311) and for the 2 mg tablet (lot MD-312) were satisfactory.

Stability data were recorded from tablets packaged in commercial 30 tablets & 100 tablets size 60 cc HDPE bottles with CRC caps, and 100 tablets in 60 cc HDPE bottles, 1000 tablets in 225 cc HDPE bottles & 5000 tablets in 1250 cc HDPE bottles, with metal screw-on caps. A 500 tablet size 150 cc HDPE bottle with metal caps was not placed on stability.

All stability data is satisfactory.

LABELING:

Labels and labeling found acceptable on 1/10/97.

STERILIZATION VALIDATION (IF APPLICABLE):

N/A

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.)

Lot # ND-312, 2 mg Estazolam tablet. Lot size cablets. Estazolam Drug Substance is supplied by DMF was found adequate on 5/7/97.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH WERE THEY MANUFACTURED BY THE SAME PROCESS?)

Batch # ND-311, 1 mg Estazolam tablet. Lot size tablets. Lot # ND-311 was manufactured by the same method as lot ND-312.

PROPOSED PRODUCTION BATCHES - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?

1 mg and 2 mg Estazolam Tablets = cablets.

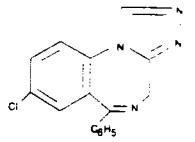
Manufacturing process is the same as the bio/stability batches.

Prepared by Stephen Sherken/6/13/97
Michael Smela/6/13/97

ESTAZOLAM TABLETS C-IV

DESCRIPTION

Estazolam, a triazolobenzodiazepine derivative, is an oral hypnotic agent. It is chemically designated as 8-chloro-6-phenyl-4H-s-triazolo[4,3-α] [1,4]benzodiazepine and has the following structural formula:



$C_{16}H_{11}ClN_4$

M. W. 294.75

Estazolam occurs as a fine, white, odorless powder that is soluble in alcohol and practically insoluble in water. Each tablet, for oral administration, contains 1 mg or 2 mg of estazolam. In addition, each tablet has the following inactive ingredients: anhydrous lactose, colloidal silicon dioxide, corn starch, lactose monohydrate and magnesium stearate. In addition, the 2 mg contains yellow iron oxide and red iron oxide.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Estazolam tablets have been found to be equivalent in absorption to an orally administered solution of estazolam. Independent of concentration, estazolam in plasma is 93% protein bound.

In healthy subjects who received up to three times the recommended dose of estazolam, peak estazolam plasma concentrations occurred within two hours after dosing (range 0.5 to 6 hours) and were proportional to the administered dose, suggesting linear pharmacokinetics over the dosage range tested.

The range of estimates for the mean elimination half-life of estazolam varied from 10 to 24 hours. The clearance of benzodiazepines is accelerated in smokers compared to nonsmokers, and there is evidence that this occurs with estazolam. This decrease in half-life, presumably due to enzyme induction by smoking, is consistent with other drugs with similar hepatic clearance characteristics. In all subjects and at all doses, the mean elimination half-life appeared to be independent of the dose.

In a small study (N=8) using various doses in older subjects (59 to 68 years), peak estazolam concentrations were found to be similar to those observed in younger subjects with a mean elimination half-life of 18.4 hours (range 13.5 to 34.6 hours).

Estazolam is extensively metabolized, and the metabolites are excreted primarily in the urine. Less than 5% of a 2 mg dose of estazolam is excreted unchanged in the urine, with only 4% of the dose appearing in the feces. 4'-hydroxy estazolam is the major metabolite in plasma, with concentrations approaching 12% of those of the parent eight hours after administration. While it and the lesser metabolite, 1-oxo-estazolam, have some pharmacologic activity, their low potencies and low concentrations preclude any significant contribution to the hypnotic effect of estazolam.

Postulated relationship between elimination rate of benzodiazepine hypnotics and their profile of common untoward effects

The type and duration of hypnotic effects and the profile of unwanted effects during administration of benzodiazepine drugs may be influenced by the biologic half-life of administered drug and any active metabolites formed. If half-lives are long, drug or metabolites may accumulate during periods of nightly administration and may be associated with impairments of cognitive and/or motor performance during waking hours; the possibility of interaction with other psychoactive drugs or alcohol will be increased. In contrast, if half-lives are short, drug and metabolites will be cleared before the next dose is ingested, and carry-over effects related to excessive sedation or CNS depression should be minimal or absent. However, during nightly use for an extended period, pharmacodynamic tolerance or adaptation to some effects of benzodiazepine hypnotics may develop. If the drug has a short elimination half-life, it is possible that a relative deficiency of the drug or its active metabolites (i.e., in relationship to the receptor site) may occur at some point in the interval between each night's use. This sequence of events may account for two clinical findings reported to occur after several weeks of nightly use of rapidly eliminated benzodiazepine hypnotics, namely, increased wakefulness during the last third of the night and increased daytime anxiety in selected patients.

Controlled Trials Supporting Efficacy

In three 7-night, double-blind, parallel-group trials comparing estazolam 1 mg and/or 2 mg with placebo in adult outpatients with chronic insomnia, estazolam 2 mg was consistently superior to placebo in subjective measures of sleep induction (latency) and sleep maintenance (duration, number of awakenings, depth and quality of sleep); estazolam 1 mg was similarly superior to placebo on all measures of sleep maintenance, however, it significantly improved sleep induction in only one of two studies. In a similarly designed trial comparing estazolam 0.5 mg and 1 mg with placebo in geriatric outpatients with chronic insomnia, only the 1 mg estazolam dose was consistently superior to placebo in sleep induction (latency) and in only one measure of sleep maintenance (i.e., duration of sleep).

In a single-night, double-blind, parallel-group trial comparing estazolam 2 mg and placebo in patients admitted for elective surgery and requiring sleep medications, estazolam was superior to placebo in subjective measures of sleep induction and maintenance.

In a 12-week, double-blind, parallel-group trial including a comparison of estazolam 2 mg and placebo in adult outpatients with chronic insomnia, estazolam was superior to placebo in subjective measures of sleep induction (latency) and maintenance (duration, number of awakenings, total wake time during sleep) at week 2, but produced consistent improvement over 12 weeks only for sleep duration and total wake time during sleep. Following withdrawal at week 12, rebound insomnia was seen at the first withdrawal week, but there was no difference between drug and placebo by the second withdrawal week in all parameters except latency, for which normalization did not occur until the fourth withdrawal week.

Adult outpatients with chronic insomnia were evaluated in a sleep laboratory trial comparing four doses of estazolam (0.25, 0.5, 1 and 2 mg) and placebo, each administered for 2 nights in a crossover design. The higher estazolam doses were superior to placebo in most EEG measures of sleep induction and maintenance, especially at the 2 mg dose, but only for sleep duration in subjective measures of sleep.

INDICATIONS AND USAGE

Estazolam tablets are indicated for the short-term management of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings. Both outpatient studies and a sleep laboratory study have shown that estazolam administered at bedtime improved sleep induction and sleep maintenance (see **CLINICAL PHARMACOLOGY**).

Because insomnia is often transient and intermittent, the prolonged administration of estazolam is generally neither necessary nor recommended. Since insomnia may be a symptom of several other disorders, the possibility that the complaint may be related to a condition for which there is a more specific treatment should be considered.

There is evidence to support the ability of estazolam to enhance the duration and quality of sleep for intervals up to 12 weeks (see **CLINICAL PHARMACOLOGY**).

CONTRAINDICATIONS

Benzodiazepines may cause fetal damage when administered during pregnancy. An increased risk of congenital malformations associated with the use of diazepam and chlordiazepoxide during the first trimester of pregnancy has been suggested in several studies. Transplacental distribution has resulted in neonatal CNS depression and also withdrawal phenomena following the ingestion of therapeutic doses of a benzodiazepine hypnotic during the last weeks of pregnancy.

Estazolam is contraindicated in pregnant women. If there is a likelihood of the patient becoming pregnant while receiving estazolam she should be warned of the potential risk to the fetus and instructed to discontinue the drug prior to becoming pregnant. The possibility that a woman of childbearing potential is pregnant at the time of institution of therapy should be considered.

WARNINGS

Estazolam, like other benzodiazepines, has CNS depressant effects. For this reason, patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness, such as operating machinery or driving a motor vehicle, after ingesting the drug, including potential impairment of the performance of such activities that may occur the day following ingestion of estazolam. Patients should also be cautioned about possible combined effects with alcohol and other CNS depressant drugs. As with all benzodiazepines, amnesia, paradoxical reactions (e.g., excitement, agitation, etc.), and other adverse behavioral effects may occur unpredictably.

There have been reports of withdrawal signs and symptoms of the type associated with withdrawal from CNS depressant drugs following the rapid decrease or the abrupt discontinuation of benzodiazepines (see **DRUG ABUSE AND DEPENDENCE**).

PRECAUTIONS

General

Impaired motor and/or cognitive performance attributable to the accumulation of benzodiazepines and their active metabolites following several days of repeated use at their recommended doses is a concern in certain vulnerable patients (e.g., those especially sensitive to the effects of benzodiazepines or those with a reduced capacity to metabolize and eliminate them)(see **DOSAGE AND ADMINISTRATION**).

Elderly or debilitated patients and those with impaired renal or hepatic function should be cautioned about these risks and advised to monitor themselves for signs of excessive sedation or impaired conditions.

Estazolam appears to cause dose-related respiratory depression that is ordinarily not clinically relevant at recommended doses in patients with normal respiratory function. However, patients with compromised respiratory function may be at risk and should be monitored appropriately. As a class, benzodiazepines have the capacity to depress respiratory drive; there are insufficient data available, however, to characterize their relative potency in depressing respiratory drive at clinically recommended doses.

As with other benzodiazepines, estazolam should be administered with caution to patients exhibiting signs or symptoms of depression. Suicidal tendencies may be present in such patients and protective measures may be required. Intentional overdosage is more common in this group of patients; therefore, the least amount of drug that is feasible should be prescribed for the patient at any one time.

Information for Patients

To assure the safe and effective use of estazolam, the following information and instructions should be given to patients:

1. Inform your physician about any alcohol consumption and medicine you are taking now, including drugs you may buy without a prescription. Alcohol should not be used during treatment with hypnotics.
2. Inform your physician if you are planning to become pregnant, if you are pregnant, or if you become pregnant while you are taking this medicine.
3. You should not take this medicine if you are nursing, as the drug may be excreted in breast milk.
4. Until you experience the way this medicine affects you, do not drive a car, operate potentially dangerous machinery, or engage in hazardous occupations requiring complete mental alertness after taking this medicine.
5. Since benzodiazepines may produce psychological and physical dependence, you should not increase the dose before consulting your physician. In addition, since the abrupt discontinuation of estazolam may be associated with temporary sleep disturbances, you should consult your physician before abruptly discontinuing doses of 2 mg per night or more.

Laboratory Tests

Laboratory tests are not ordinarily required in otherwise healthy patients. When treatment with estazolam is protracted, periodic blood counts, urinalyses, and blood chemistry analyses are advisable.

Drug Interactions

If estazolam is given concomitantly with other drugs acting on the central nervous system, careful consideration should be given to the pharmacology of all agents. The action of the benzodiazepines may be potentiated by anticonvulsants, antihistamines, alcohol, barbiturates, monoamine oxidase inhibitors, narcotics, phenothiazines, psychotropic medications, or other drugs that produce CNS depression. Smokers have an increased clearance of benzodiazepines as compared to nonsmokers; this was seen in studies with estazolam (see **CLINICAL PHARMACOLOGY**).

Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year carcinogenicity studies were conducted in mice and rats at dietary doses of 0.8, 3, and 10 mg/kg/day and 0.5, 2, and 10 mg/kg/day, respectively. Evidence of tumorigenicity was not observed in either study. Incidence of hyperplastic liver nodules increased in female mice given the mid- and high-dose levels. The significance of such nodules in mice is not known at this time.

In vitro and *in vivo* mutagenicity tests including the Ames test, DNA repair in *B. subtilis*, *in vivo* cytogenetics in mice and rats, and the dominant lethal test in mice did not show a mutagenic potential for estazolam.

Fertility in male and female rats was not affected by doses up to 30 times the usual recommended human dose.

Pregnancy

1. ***Teratogenic Effects***
   Pregnancy Category X (see **CONTRAINDICATIONS**).
2. ***Nonteratogenic Effects***
   The child born of a mother taking benzodiazepines may be at some risk for withdrawal symptoms during the postnatal period. Neonatal flaccidity has been reported in an infant born of a mother who received benzodiazepines during pregnancy.

Labor and Delivery

Estazolam has no established use in labor or delivery.

Nursing Mothers

Human studies have not been conducted; however, studies in lactating rats indicate that estazolam and/or its metabolites are secreted in the milk. The use of estazolam in nursing mothers is not recommended.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 18 have not been established.

Geriatric Use

Approximately 18% of individuals participating in the premarketing clinical trials of estazolam were 60 years of age or older. Overall, the adverse event profile did not differ substantively from that observed in younger individuals. Care should be exercised when prescribing benzodiazepines to small or debilitated elderly patients (see **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS

Commonly Observed

The most commonly observed adverse events associated with the use of estazolam, not seen at an equivalent incidence among placebo-treated patients were somnolence, hypokinesia, dizziness, and abnormal coordination.

Associated with Discontinuation of Treatment

Approximately 3% of 1277 patients who received estazolam in U.S. premarketing clinical trials discontinued treatment because of an adverse clinical event. The only event commonly associated with discontinuation, accounting for 1.3% of the total, was somnolence.

Incidence in Controlled Clinical Trials

The table below enumerates adverse events that occurred at an incidence of 1% or greater among patients with insomnia who received estazolam in 7-night, placebo-controlled trials. Events reported by investigators were classified into standard dictionary (COSTART) terms to establish event frequencies.

ESTAZOLAM TABLETS 0199-01

0199-01 ESTAZOLAM TABLETS

Event frequencies reported were not corrected for the occurrence of these events at baseline. The frequencies were obtained from data pooled that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice in which patient characteristics and other factors differ from those that prevailed in these six clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigators involving related drug products and uses since each group of drug trials was conducted under a different set of conditions. However, the cited figures provide the physician with a basis of estimating the across six studies. estazolam, N=685; placebo, N=433. The prescriber should be aware relative contribution of drug and nondrug factors to the incidence of side effects in the population studied.

INCIDENCE OF ADVERSE EXPERIENCES IN PLACEBO-CONTROLLED CLINICAL TRIALS
(Percentage of Patients Reporting)

Body System/ Adverse Event*	Estazolam (N=685)	Placebo (N=433)
Body as a Whole		
Headache	16	27
Asthenia	11	8
Malaise	5	5
Lower extremity pain	3	2
Back pain	2	2
Body pain	2	2
Abdominal pain	1	2
Chest Pain	1	1
Digestive System		
Nausea	4	5
Dyspepsia	2	2
Musculoskeletal System		
Stiffness	1	-
Nervous System		
Somnolence	42	27
Hypokinesia	8	4
Nervousness	8	11
Dizziness	7	3
Coordination abnormal	4	1
Hangover	3	2
Confusion	2	-
Depression	2	3
Dream abnormal	2	2
Thinking abnormal	2	1
Respiratory System		
Cold symptoms	3	5
Pharyngitis	1	2
Skin and Appendages		
Pruritus	1	-

*Events reported by at least 1% of estazolam patients.

Other Adverse Events

During clinical trials conducted by Abbott, some of which were not placebo-controlled, estazolam was administered to approximately 1300 patients. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals experiencing adverse events, similar types of untoward events must be grouped into a smaller number of standardized event categories. In the tabulations that follow, a standard COSTART dictionary terminology has been used to classify reported adverse events. The frequencies presented, therefore, represent the proportion of the 1277 individuals exposed to estazolam who experienced an event of the type cited on at least one occasion while receiving estazolam. All reported events are included except those already listed in the previous table, those COSTART terms too general to be informative, and those events where a drug cause was remote. Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in less than 1/1000 patients. It is important to emphasize that, although the events reported did occur during treatment with estazolam, they were not necessarily caused by it.

Body as a Whole

Infrequent

Allergic reaction, chills, fever, neck pain, upper extremity pain

Rare

Edema, jaw pain, swollen breast

Cardiovascular System

Infrequent

Flushing, palpitation

Rare

Arrhythmia, syncope

Digestive System

Frequent

Constipation, dry mouth

Infrequent

Decreased appetite, flatulence, gastritis, increased appetite, vomiting

Rare

Enterocolitis, melena, ulceration of the mouth

Endocrine System

Rare

Thyroid nodule

Hematologic and Lymphatic System

Rare

Leukopenia, purpura, swollen lymph nodes

Metabolic/Nutritional Disorders

Infrequent

Thirst

Rare

Increased SGOT, weight gain, weight loss

Musculoskeletal System

Infrequent

Arthritis, muscle spasm, myalgia

Rare

Arthralgia

Nervous System

Frequent

Anxiety

Infrequent

Agitation, amnesia, apathy, emotional lability, euphoria, hostility, paresthesia, seizure, sleep disorder, stupor, twitch

Rare

Ataxia, circumoral paresthesia, decreased libido, decreased reflexes, hallucinations, neuritis, nystagmus, tremor

Minor Changes in EEG patterns, usually low-voltage fast activity, have been observed in patients during estazolam therapy or withdrawal and are of no known clinical significance.

Respiratory System

Infrequent

Asthma, cough, dyspnea, rhinitis, sinusitis

Rare

Epistaxis, hyperventilation, laryngitis

Skin and Appendages

Infrequent

Rash, sweating, urticaria

Rare

Acne, dry skin

Special Senses

Infrequent

Abnormal vision, ear pain, eye irritation, eye pain, eye swelling, perverse taste, photophobia, tinnitus

Rare

Decreased hearing, diplopia, scotomata

Urogenital System

Infrequent

Frequent urination, menstrual cramps, urinary hesitancy, urinary urgency, vaginal discharge/itching

Rare

Hematuria, nocturia, oliguria, penile discharge, urinary incontinence

Postintroduction Reports

Voluntary reports of non-U.S. postmarketing experience with estazolam have included rare occurrences of photosensitivity and agranulocytosis. Because of the uncontrolled nature of these spontaneous reports, a causal relationship to estazolam treatment has not been determined.

DRUG ABUSE AND DEPENDENCE

Controlled Substance

Estazolam tablets are a controlled substance in Schedule IV.

Abuse and Dependence

Withdrawal symptoms similar to those noted with sedatives/hypnotics and alcohol have occurred following the abrupt discontinuation of drugs in the benzodiazepine class. The symptoms can range from mild dysphoria and insomnia to a major syndrome that may include abdominal and muscle cramps, vomiting, sweating, tremors, and convulsions.

Although withdrawal symptoms are more commonly noted after the discontinuation of higher than therapeutic doses of benzodiazepines, a proportion of patients taking benzodiazepines chronically at therapeutic doses may become physically dependent on them. Available data, however, cannot provide a reliable estimate of the incidence of dependency or the relationship of the dependency to dose and duration of treatment. There is some evidence to suggest that gradual reduction of dosage will attenuate or eliminate some withdrawal phenomena. In most instances, withdrawal phenomena are relatively mild and transient; however, life-threatening events (e.g., seizures, delirium, etc.) have been reported.

Gradual withdrawal is the preferred course for any patient taking benzodiazepines for a prolonged period. Patients with a history of seizures, regardless of their concomitant antiseizure drug therapy, should not be withdrawn abruptly from benzodiazepines.

Individuals with a history of addiction to or abuse of drugs or alcohol should be under careful surveillance when receiving benzodiazepines because of the risk of habituation and dependence to such patients.

OVERDOSAGE

As with other benzodiazepines, experience with estazolam indicates that manifestations of overdosage include somnolence, respiratory depression, confusion, impaired coordination, slurred speech, and ultimately, coma. Patients have recovered from overdosage as high as 40 mg. As in the management of intentional overdose with any drug, the possibility should be considered that multiple agents may have been taken.

Gastric evacuation, either by the induction of emesis, lavage, or both, should be performed immediately. Maintenance of adequate ventilation is essential. General supportive care, including frequent monitoring of the vital signs and close observation of the patient, is indicated. Fluids should be administered intravenously to maintain blood pressure and encourage diuresis. The value of dialysis in treatment of benzodiazepine overdose has not been determined. The physician may wish to consider contacting a Poison Control Center for up-to-date information on the management of hypnotic drug product overdose.

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.

DOSAGE AND ADMINISTRATION

The recommended initial dose for adults is 1 mg at bedtime; however, some patients may need a 2 mg dose. In healthy elderly patients, 1 mg is also the appropriate starting dose, but increases should be initiated with particular care. In small or debilitated older patients, a starting dose of 0.5 mg, while only marginally effective in the overall elderly population, should be considered.

HOW SUPPLIED

Estazolam tablets are available as white, square, flat-faced, beveled-edge, scored tablets, debossed "Z" above the bisect, "1" below the bisect on one side, and "4036" on the other containing 1 mg estazolam packaged in bottles of 30, 100, 500, 1000 and 5000 tablets.

Estazolam tablets are available as salmon-colored, square, flat-faced, beveled-edge, scored tablets, debossed "Z" above the bisect, "2" below the bisect on one side, and "4037" on the other containing 2 mg estazolam packaged in bottles of 30, 100, 500, 1000 and 5000 tablets.

PHARMACIST: Dispense in a tight container as defined in the USP. Use child-resistant closure (as required).

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

CAUTION: Federal law prohibits dispensing without prescription.

MANUFACTURED BY
ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309

0172
12/96
D1

ESTAZOLAM TABLETS

Zenith Goldline

NDC 0172-4036-46

ESTAZOLAM

TABLETS

1 mg

50 TABLETS (White)

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

CAUTION: Federal law prohibits dispensing without prescription.

USUAL DOSAGE: See Package Insert

PHARMACIST: Dispense in a tight container as defined in the USP. Use child-resistant closure (as required).

NDC 0172-4036-46

Each Tablet Contains:
Estazolam 1 mg

Manufactured by:
ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309

0896J

N 3 0172-4036-46 8

LOT:

EXP:

Zenith Goldline

NDC 0172-4036-60

ESTAZOLAM

TABLETS

1 mg

100 TABLETS (White)

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

CAUTION: Federal law prohibits dispensing without prescription.

USUAL DOSAGE: See Package Insert

PHARMACIST: Dispense in a tight container as defined in the USP. Use child-resistant closure (as required).

NDC 0172-4036-60

Each Tablet Contains:
Estazolam 1 mg

Manufactured by:
ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309

0896J

N 3 0172-4036-60 4

LOT:

EXP:

Zenith Goldline

NDC 0172-4036-70

ESTAZOLAM

TABLETS

1 mg

500 TABLETS (White)

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

CAUTION: Federal law prohibits dispensing without prescription.

USUAL DOSAGE: See Package Insert

PHARMACIST: Dispense in a tight container as defined in the USP. Use child-resistant closure (as required).

NDC 0172-4036-70

Each Tablet Contains:
Estazolam 1 mg

Manufactured by:
ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309

0896J

N 3 0172-4036-70 3

LOT:

EXP:

Zenith Goldline

NDC 0172-4036-80

ESTAZOLAM

TABLETS

1 mg

1000 TABLETS (White)

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

CAUTION: Federal law prohibits dispensing without prescription.

USUAL DOSAGE: See Package Insert

PHARMACIST: Dispense in a tight container as defined in the USP. Use child-resistant closure (as required).

NDC 0172-4036-80

Each Tablet Contains:
Estazolam 1 mg

Manufactured by:
ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309

0896J

N 3 0172-4036-80 2

LOT:

EXP:

Zenith Goldline

NDC 0172-4036-85

ESTAZOLAM

TABLETS

1 mg

5000 TABLETS (White)

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

CAUTION: Federal law prohibits dispensing without prescription.

USUAL DOSAGE: See Package Insert

PHARMACIST: Dispense in a tight container as defined in the USP. Use child-resistant closure (as required).

NDC 0172-4036-85

Each Tablet Contains:
Estazolam 1 mg

Manufactured by:
ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309

0896J

N 3 0172-4036-85 7

LOT:

EXP:

Zenith Goldline

NDC 0172-4036-46

ESTAZOLAM

TABLETS

1 mg

C IV

30 TABLETS (White)

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

CAUTION: Federal law prohibits dispensing without prescription.

USUAL DOSAGE: See Package Insert

PHARMACIST: Dispense in a tight container as defined in the USP. Use child-resistant closure (as required).

NDC 0172-4036-46

Each Tablet Contains:
Estazolam 1 mg

Manufactured by:
ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309

0896J

N 3 0172-4036-46 8

LOT:

EXP:

Zenith Goldline

NDC 0172-4036-60

ESTAZOLAM

TABLETS

1 mg

C IV

100 TABLETS (White)

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

CAUTION: Federal law prohibits dispensing without prescription.

USUAL DOSAGE: See Package Insert

PHARMACIST: Dispense in a tight container as defined in the USP. Use child-resistant closure (as required).

NDC 0172-4036-60

Each Tablet Contains:
Estazolam 1 mg

Manufactured by:
ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309

0896J

N 3 0172-4036-60 4

LOT:

EXP:

Zenith Goldline

NDC 0172-4036-70

ESTAZOLAM

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NDC 0172-4036-70

Each Tablet Contains:
Estazolam 1 mg

Manufactured by:
ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309

0896J

N 3 0172-4036-70 3

LOT:

EXP:

Zenith Goldline

NDC 0172-4036-80

ESTAZOLAM

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NDC 0172-4036-80

Each Tablet Contains:
Estazolam 1 mg

Manufactured by:
ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309

0896J

N 3 0172-4036-80 2

LOT:

EXP:

Zenith Goldline

NDC 0172-4036-85

ESTAZOLAM

TABLETS

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C IV

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

CAUTION: Federal law prohibits dispensing without prescription.

USUAL DOSAGE: See Package Insert

PHARMACIST: Dispense in a tight container as defined in the USP. Use child-resistant closure (as required).

NDC 0172-4036-85

Each Tablet Contains:
Estazolam 1 mg

Manufactured by:
ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309

0896J

N 3 0172-4036-85 7

LOT:

EXP:

00150

Zenith Goldline

NDC 0172-4036-46

ESTAZOLAM

TABLETS

1 mg

30 TABLETS (White)

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

CAUTION: Federal law prohibits dispensing without prescription.

USUAL DOSAGE: See Package Insert

PHARMACIST: Dispense in a tight container as defined in the USP. Use child-resistant closure (as required).

NDC 0172-4036-46

Each Tablet Contains:
Estazolam 1 mg

Manufactured by:
ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309

0896J

N 3 0172-4036-46

LOT:

EXP:

Zenith Goldline

NDC 0172-4036-60

ESTAZOLAM

TABLETS

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NDC 0172-4036-60

Each Tablet Contains:
Estazolam 1 mg

Manufactured by:
ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309

0896J

N 3 0172-4036-60 4

LOT:

EXP:

Zenith Goldline

NDC 0172-4036-70

ESTAZOLAM

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LOT:

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NDC 0172-4036-80

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0896J

N 3 0172-4036-80 2

LOT:

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NDC 0172-4036-85

ESTAZOLAM

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NDC 0172-4036-85

Each Tablet Contains:
Estazolam 1 mg

Manufactured by:
ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309

0896J

N 3 0172-4036-85 7

LOT:

EXP:

00756

Zenith Goldline

NDC 0172-**4037**-46

ESTAZOLAM

TABLETS

2 mg

30 TABLETS (Salmon)

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

CAUTION: Federal law prohibits dispensing without prescription.

USUAL DOSAGE: See Package Insert

PHARMACIST: Dispense in a tight container as defined in the USP. Use child-resistant closure (as required).

NDC 0172-4037-46

Each Tablet Contains:
Estazolam 2 mg

Manufactured by:
ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309

0896J

N 3 0172-4037-46 5

LOT:

EXP:

Zenith Goldline

NDC 0172-**4037**-60

ESTAZOLAM

TABLETS

2 mg

100 TABLETS (Salmon)

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

CAUTION: Federal law prohibits dispensing without prescription.

USUAL DOSAGE: See Package Insert

PHARMACIST: Dispense in a tight container as defined in the USP. Use child-resistant closure (as required).

NDC 0172-4037-60

Each Tablet Contains:
Estazolam 2 mg

Manufactured by:
ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309

0896J

N 3 0172-4037-60 1

LOT:

EXP:

Zenith Goldline

NDC 0172-**4037**-70

ESTAZOLAM

TABLETS

2 mg

500 TABLETS (Salmon)

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

CAUTION: Federal law prohibits dispensing without prescription.

USUAL DOSAGE: See Package Insert

PHARMACIST: Dispense in a tight container as defined in the USP. Use child-resistant closure (as required).

NDC 0172-4037-70

Each Tablet Contains:
Estazolam 2 mg

Manufactured by:
ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309

0896J

N 3 0172-4037-70 0

LOT:

EXP:

Zenith Goldline

NDC 0172-**4037**-80

ESTAZOLAM

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

CAUTION: Federal law prohibits dispensing without prescription.

USUAL DOSAGE: See Package Insert

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Estazolam 2 mg

Manufactured by:
ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309

0896J

N 3 0172-4037-80 9

LOT:

EXP:

Zenith Goldline

NDC 0172-**4037**-85

ESTAZOLAM

TABLETS

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

CAUTION: Federal law prohibits dispensing without prescription.

USUAL DOSAGE: See Package Insert

PHARMACIST: Dispense in a tight container as defined in the USP. Use child-resistant closure (as required).

NDC 0172-4037-85

Each Tablet Contains:
Estazolam 2 mg

Manufactured by:
ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309

0896J

N 3 0172-4037-85 4

LOT:

EXP:

0076C

Zenith Goldline

NDC 0172-4037-46

ESTAZOLAM

TABLETS

2 mg

C IV

30 TABLETS (Salmon)

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

CAUTION: Federal law prohibits dispensing without prescription.

USUAL DOSAGE: See Package Insert

PHARMACIST: Dispense in a tight container as defined in the USP. Use child-resistant closure (as required).

NDC 0172-4037-46

Each Tablet Contains:
Estazolam 2 mg

Manufactured by:
ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309

0896J

N 3 0172-4037-46 5

1997

LOT:

EXP:

Zenith Goldline

NDC 0172-4037-60

ESTAZOLAM

TABLETS

2 mg

C IV

100 TABLETS (Salmon)

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

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Each Tablet Contains:
Estazolam 2 mg

Manufactured by:
ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309

0896J

N 3 0172-4037-60 1

1997

LOT:

EXP:

Zenith Goldline

NDC 0172-4037-70

ESTAZOLAM

TABLETS

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C IV

500 TABLETS (Salmon)

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FT. LAUDERDALE, FL 33309

0896J

N 3 0172-4037-70 0

1997

LOT:

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Zenith Goldline

NDC 0172-4037-80

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FT. LAUDERDALE, FL 33309

0896J

N 3 0172-4037-80 9

1997

LOT:

EXP:

Zenith Goldline

NDC 0172-4037-85

ESTAZOLAM

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ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309

0896J

N 3 0172-4037-85 4

1997

LOT:

EXP:

0076d

Zenith Goldline

NDC 0172-4037-46

ESTAZOLAM

TABLETS

2 mg

30 TABLETS (Salmon)

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

CAUTION: Federal law prohibits dispensing without prescription.

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Estazolam 2 mg

Manufactured by:
ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309

0896J

N 3 0172-4037-46 5

LOT:

EXP:

Zenith Goldline

NDC 0172-4037-60

ESTAZOLAM

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FT. LAUDERDALE, FL 33309

0896J

N 3 0172-4037-60 1

LOT:

EXP:

Zenith Goldline

NDC 0172-4037-70

ESTAZOLAM

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FT. LAUDERDALE, FL 33309

0896J

N 3 0172-4037-80 9

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NDC 0172-4037-85

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ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309

0896J

N 3 0172-4037-85 4

LOT:

EXP:

0076e

DN

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 74826

SPONSOR :Zenith Pharmaceuticals

DRUG & DOSAGE FORM : Estazolam Tablet
STRENGTH (s) : 2 mg, 1 mg
TYPE OF STUDY: SD SDF MD OTHER
STUDY SITE: CLINICAL : ANALYTICAL

STUDY SUMMARY : 2 mg Fasting Study Estazolam

Parameter	test	ref	ratio	CI
LAUC(0-T) ngxhr/ml	1963.8	1920.1	1.02	99-106
LAUC(0-Inf)ngxhr/ml	2097.7	2062.1	1.02	98-106
Lcmax(ng/ml)	87.3	85.5	1.02	97-107
Tmax hr	1.6	1.6		
Half-life hr	17.7	18.4		

DISSOLUTION : Paddle 50 RPM, 900 ml Water,NLT in 30 min
Conditions: This is an FDA method, 2 mg strength

Time(min)	Test Mean(range)	Ref. Mean(range)
10	102	88.7
20	102	96.3
30	102	98.7
45	102	99.8
60	102	100

PRIMARY REVIEWER, :Andre Jackson BRANCH :I

INITIAL :_ DATE : 6/30/97

Team Leader : Y.C. Huang BRANCH :I

INITIAL : DATE : 6/30/97

for DIRECTOR:Nicholas Fleischer
DIVISION OF BIOEQUIVALENCE

INITIAL : DATE : 6/30/97

9.3

ANDA 74-826

MAY 23 1996

Zenith Laboratories, Inc.
Attention: Robert J. Monaghan
140 Legrand Avenue
Northvale NJ 07647

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 Estazolam Tablets USP, 1 mg, 2 mg.

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

2. The following dissolution testing will need to be incorporated into your stability and quality control programs:

   The dissolution testing should be conducted in 900 ml of water at 37°C using USP 23 apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

   Not less than of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

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,

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

0.1

MAY 20 1996

Estazolam
2 mg Tablet
1 mg Tablet
ANDA# 74826
Reviewer: Andre J. Jackson
WP #74826SDW.D95

Zenith Pharmaceuticals
Northvale, New Jersey
Submission Dated:
December 29, 1995

REVIEW OF FASTING 2 MG TABLET BIOEQUIVALENCE STUDY, DISSOLUTION DATA and WAIVER REQUEST FOR 1 mg TABLET

Background

Estazolam is a triazolobenzodiazepine derivative. Its likely mechanism of action involves displacement of GABA at the GABA and benzodiazepine receptor complex, allowing for a more efficient opening of the chloride ionophore. Estazolam is indicated for the short term management of insomnia, frequent nocturnal awakenings, and/or early morning awakenings.

In healthy subjects who received up to three times the recommended dose of estazolam, peak estazolam plasma concentrations occurred within two hours after dosing and were proportional to the administered dose, suggesting linear kinetics over the investigated dose range. The range of estimates for the mean elimination half-life of estazolam varied from 10 to 24 hours. The clearance of benzodiazepines is accelerated in smokers compared to nonsmokers, and there is evidence that this occurs with estazolam.

The recommended initial dosing regimen for adults is 1 mg once daily at bedtime, although some patients may require a dose of 2 mg once daily. Estazolam is marketed in the U.S. by Abbott Laboratories as Prosom® as 1 and 2 mg strength tablets.

Objective:

The aim of this study is to compare the rate and extent of estazolam tablets manufactured by Zenith Pharmaceuticals with a commercial lot of the reference product, Prosom® tablets manufactured by Abbott Laboratories following a single 2mg dose.

Methods:

The study was conducted at
under the direction of
. The samples were analyzed by
under the direction of
Phase I was conducted on November 7, 1995, while phase II was done November 17, 1995. Sample analysis was done between November 28, 1995, and December 14, 1995. Total sample storage time was less than 60 days.

I. Characterization of Study Group:

A. Inclusion criteria

1. All volunteers selected for this study were male volunteers between the ages of 18 and 45 years. Weight range of the volunteers was within 15% of normal body weight relative to height and frame size as per 1983 Metropolitan Height and Weight Table.

2. Each volunteer was given a general physical examination within 30 days of initiation of the study. Each examination included blood pressure, general observations, history, complete hemogram (hemoglobin, hematocrit, WBC, differential), urinalysis (including microscopic), biochemistry (blood urea nitrogen, serum bilirubin [total]), HIV antibody screen, hepatitis B surface antigen screens. Volunteers selected for the study had no clinically significant abnormal findings.

3. Normal electrocardiogram.

4. Have provided written informed consent.

B. Exclusion Criteria

1. Volunteers with a history of alcohol or drug addiction during the past two years, gastrointestinal, renal, hepatic or cardiovascular diseases, tuberculosis, epilepsy, asthma or any other medical disorder requiring medication.

2. Any noted EKG abnormality.

3. Hypersensitivity or idiosyncratic reaction to estazolam or any other benzodiazepine.

4. Participation in a previous clinical trial or the donation of 900 ml or more of blood within the past 30 days.

5. Use of any prescription drug during the two week period prior to study initiation, or any OTC drug during the one week period prior to study initiation.

6. Positive screen for drugs of abuse.

7. Subjects that have used nicotine products within the last 3 months.

8. Subjects that have an abnormal diet during the 4 weeks preceding the study.

9. Inability to refrain from the consumption of alcohol- or xanthine-containing beverages and foods for 48 hours before dosing and throughout the period of sample collection.

C. Informed Consent

All prospective volunteers had the study explained by a member of the research team or a member of their staff. The nature of the drug substance to be evaluated was explained together with the potential hazards involving drug allergies and possible adverse reactions. An acknowledgement of the receipt of this information and the participant's freely-tendered offer to volunteer was obtained in writing from each participant in the study.

II. Study Conduct

32 subjects were screened and accepted into the study. 2 subjects dropped out the study.

A. Subjects fasted 10 hours before dosing and until 4.0 hrs after their scheduled dosing times. All subjects were given 240 ml of water at the time of drug administration. Water was not allowed from 1 hour before until 1 hour following drug administration and then provided ad libitum.

Subjects were instructed to remain seated for 4 hours following study drug administration, and not to engage in any strenuous physical activity.

Standard meals were provided at 4 and approximately 10 hours after dosing.

B. The products employed in the study were:

1. Test: Zenith Pharmaceuticals 2 mg estazolam tablet, Lot # ND-312, potency 100.5%, proposed expiration date 9/97, lot size tablets.

2. Reference product: Abbott Laboratories 2 mg Prosom[R] tablet, Lot # 88-871-AA-21, potency 102.0%, expiration date July 1, 1997.

There was a 10 day washout between doses.

C. A 2 mg dose (1 x 2 mg) of each product (test and reference) was administered at time zero with 240 ml of water. The randomization scheme is presented in Table 1.

Table 1. Random Assignment of 32 subjects

Sequence	SUBJECT
A,B	3,4,5,7,11,12,13,15,18,20,22,23,25,26,29,30
B,A	1,2,6,8,9,10,14,16,17,19,21,24,27,28,31,32

Treatment A: Zenith 1 X 2 mg estazolam tablets
Treatment B: Abbott 1 x 2 mg Prosom® tablets

The formulation for the 2 mg tablet is given in Table 2.

Table 2. COMPOSITION OF THE 2 MG Estazolam Tablet-

Ingredient	Standard	Amount/Tablet(mg)	Per Cent/Tablet
Estazolam	-	2.04[1]	1.28
Anhydrous Lactose	NF		
Starch	NF		
Lactose Monohydrate	NF		
Colloidal Silicon Dioxide	NF		
Starch	NF		
Magnesium Stearate	NF		
Yellow Pigment Blend	-		
Tablet Weight		160.0 mg	100.0%

[1.] contains 2% overage.

D. Blood samples were collected pre-dose and at the following times post-dose: 0.17, 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 9, 12, 24, 48 and 72 hours after dosing.

E. During the study subjects were monitored for adverse reactions.

III. Analytical

IV. Pharmacokinetic Methodology

Area under the curve(0-t) and AUC(0-inf) was calculated as well as elimination parameters for each subject and dosing group. Observed values for Tmax and Cmax were also reported.

V. Statistical Evaluation

ANOVA was performed at an alpha=0.05 using the GLM procedure of SAS. The model contained the effects of subject within sequence, period and treatment. Sequence effects were tested against the mean square term for subjects within sequence. All other main effects were tested against the mean square error term. The 90% confidence intervals for the difference between formulations and the power to detect a 20% difference between formulations were calculated for each parameter based upon its ANOVA.

Log-transformed data were submitted for analysis.

Results

Table 8. Estazolam plasma levels, Mean (±cv), for the subjects(N=30) that received the test and reference formulations(1x2 mg) after an overnight fast. Values are ng/ml.

	TREATMENT A Zenith-Test		TREATMENT B Abbott-Reference	
Time (hrs)	Mean	CV%	Mean	CV%
0	0.0	-	0.0	-
0.17	6.4	126	8.6	220
0.33	43.00	68	34.8	88
0.67	78.0	23	72.2	26
1.0	81.4	23	77.1	18
1.5	76.2	18	75.2	16
2.0	75.9	15	72.9	15
2.5	74.3	15	70.9	14
3.0	71.2	14	68.9	14
4.0	68.3	16	65.7	13
5.0	70.5	15	68.9	16
6.0	71.6	16	68.2	16
9.0	58.2	17	55.1	17
12.0	52.7	18	50.2	17
24.0	31.3	25	30.7	27
48.0	12.1	46	12.9	46
72.0	5.3	56	5.4	55

Table 9. Mean pharmacokinetic parameters ±% CV for subjects that received the test and reference estazolam formulations following an overnight fast.

TREATMENT				
Variable	A=Test	B=Reference	Ratio A/B	N
AUCL[2] (ng/mlxhr)	2008.5±22	1966.3±21	1.02	30
LNAUCL[4]	1963.8	1920.1	1.02	30
AUCI[3] (ng/mlxhr)	2158.6±25	2126.5±24	1.02	30
LNAUCI[4]	2097.7	2062.1	1.02	30
Cmax(ng/ml)	88.5±17	86.2±12	1.03	30
LNCmax[4]	87.3	85.5	1.02	30
KEL-1 (hr)	0.040± 18	0.040±21		
HALF (hr)	17.7	18.4		
Tmax (hr)	1.6	1.6		

[2]AUCL = AUC (0 to last measurable concentration)
[3]AUCI = AUC (0 - infinity)
[4]Log Transformed(LNAUCL,LNAUCI,LNCmax) - Ratio is Geometric Mean

Table10. 90% Confidence Intervals for estazolam based on Ln transformed data(N=30).

Ln AUC(0-t)	(99 106)
Ln AUC(0-INF)	(98 106)
Ln Cmax	(97 107)

The Confidence Intervals for estazolam were verified by the reviewer.

Adverse Effects

There were few reported adverse effects and they were mainly associated with the reference product and are presented in Table 11.

Subject Drop outs

The study began with 32 volunteers. Subjects # 11 and 32 elected to withdraw for personal reasons.

Sample Repeats

There were 7 sample repeats out of 1054 samples analyzed(0.6%). The major reason was that the original value appeared to be incongruous with surrounding data.

The firm also requested a waiver for their 1 mg tablet based upon proportionality of formulation with the 2 mg tablet. The comparative formulations are given in Table 12.

Table 12. Comparative Compositions for the 2 mg and 1 mg Estazolam Tablets

Ingredient	Standard	Amount/ Tablet (mg)	%/Tablet	Amount/ Tablet (mg)	%/Tablet
Estazolam	-	2.041[1]	1.3	1.02[1]	0.64
Anhydrous Lactose	NF				
Starch	NF				
Lactose Monohydrate	NF				
Colloidal Silicon Dioxide	NF				
Starch	NF				
Magnesium Stearate	NF				
Yellow Pigment Blend	-				
Tablet Weight		160.0 mg	100.0%	160.0 mg	100.0%

[1] contains 2% overage.

Dissolution

The dissolution study for estazolam was done as follows:

Apparatus:	Paddle, 50 RPM
Medium:	900 ml Water
No. of Units Analyzed:	12
Specifications:	NLT in 30 minutes
Assay:	

The results are presented in Table 13.

Comments:

1. The dissolution data for the test product are acceptable.

2. The 1 mg tablet is compositionally proportional to the 2 mg tablet which underwent bioequivalency testing.

3. The 90% confidence on the ln transformed parameters AUC(0-t), AUC(0-inf) and Cmax were within the acceptable ange of 80-125% of the reference.

Recommendation:

1. The bioequivalence study conducted by Zenith on its 2 mg estazolam tablet, Lot No. ND-312, comparing it to Abbott's Prosom^{R} 2 mg tablet Lot No. 88-871-AA-21 has been found to be acceptable by the Division of Bioequivalence. Therefore, Zenith's estazolam 2 mg tablet is deemed bioequivalent to Prosom^{R} 2 mg tablets manufactured by Abbott.

2. The dissolution testing conducted by Zenith on the 2 mg strength, Lot No. ND-312 and the 1 mg strength Lot No. ND-311 is acceptable. The formulation for the 1 mg tablet is compositionally proportional to the 2 mg tablet which underwent a bioequivalence study. Therefore, the waiver for the 1 mg strength is granted and the 1.0 mg estazolam tablet is deemed bioequivalent to the 1.0 mg Prosom^{R} tablet manufactured by Abbott.

3. The in vitro dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml of Water at 37^{0}C using USP 23 apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

Not less than of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

Andre Jackson, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHUANG
FT INITIALED YCHUANG _____ Date: 5/17/96

Concur: _____ Date: 5/20/96
Keith Chan, Ph.D.
Director
Division of Bioequivalence

ANDA# 74-826 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-652 (Huang, Jackson), Drug File, Division File

AJJ/040396/dbm/WP# 74826SDW.D95
1st Draft 4/3/96

Table13 . In Vitro Dissolution Testing

Drug (Generic Name):Estazolam
Dose Strength:2 mg
ANDA No.:74-826
Firm:Zenith
Submission Date:December 29, 1995
File Name:74826SDW.D95

Conditions for Dissolution Testing:

USP XXIII Basket: Paddle:x RPM: 50
No. Units Tested: 12
Medium: Water
Volume:900 ml
Specifications: NLT in 30 min

Reference Drug: Prosom
Assay Methodology

Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # ND 312 Strength(mg) 2			Reference Product Lot # 88-871-AA-21 Strength(mg) 2		
	Mean %	Range	%CV	Mean %	Range	%CV
10	102.1		1.2	88.7		2.9
20	102.2		1.2	96.3		1.6
30	102.0		1.2	98.7		1.5
45	102.0		1.2	99.8		0.9
60	102.1		1.2	100.0		1.2

Sampling Times (Minutes)	Test Product Lot # ND-311 Strength(mg) 1			Reference Product Lot # 05-144-AA-21 Strength(mg) 1		
	Mean	Range	%CV	Mean	Range	%CV
10	101.6		2.8	92.4		2.4
20	102.2		2.9	97.4		2.1
30	102.2		2.8	99.0		1.8
45	102.3		2.6	99.6		1.6
60	102.3		2.8	99.5		2.1

TABLE 11
CLINICAL COMPLAINTS

Treatment*	Subject No.	Complaint	Onset (post-dose)	Approx. Duration	Relationship to Study Therapy	Intensity
B	9	Lightheaded	14 min.	1 hr.	Possibly	Mild
B	24	Vomiting	24 min.	2 min.	Possibly	Moderate
B	27	Feels tired (less energy)	1 day 13 hrs. 8 min.	14 hrs.	Possibly	Mild
B	32	Feels tired	1 day 8 hrs. 58 min.	13 hrs.	Possibly	Mild
B	23	Feeling tired	43 min.	8 hrs. 33 min.	Probably	Mild

* A = Zenith 1 x 2 mg estazolam tablet
B = Abbott (Prosom®) 1 x 2 mg estazolam tablet