CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074818

Trade Name : ESTAZOLAM TABLETS 1MG AND 2MG

Generic Name: Estazolam Tablets 1mg and 2mg

Sponsor : Royce Laboratoriest, Inc.

Approval Date: August 19, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074818

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074818

APPROVAL LETTER

ANDA 74-818

AUG 19 1997

Royce Laboratories, Inc.
Attention: Mr. William Stahovec
16600 N.W. 54 Avenue
Miami, FL 33014

Dear Sir:

This is in reference to your abbreviated new drug application dated December 27, 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 June 18 and July 28, 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.

Validation of the regulatory methods has not been completed. It is the policy of the Office not to withhold approval until the validation is complete. We acknowledge your commitment to satisfactorily resolve any deficiencies which may be identified.

Sincerely yours,

for 8-19-97

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074818

FINAL PRINTED LABELING

NDC 51875-0421-1

Royce

ESTAZOLAM TABLETS

C IV

2 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 Tablets

Each tablet contains:
Estazolam ..... 2 mg

Usual Dosage:
See accompanying product literature.

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

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

Batch No.:

Exp. Date:

N 3 51875-0421-1 5

NDC 51875-0421-2

Royce

ESTAZOLAM TABLETS

C IV

2 mg

CAUTION: Federal law prohibits dispensing without prescription.

500 Tablets

Mfd. By: Royce Laboratories, Inc., Miami, FL 33014

Each tablet contains:
Estazolam ..... 2 mg

Usual Dosage:
See accompanying product literature.

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

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

Batch No.:

Exp. Date:

N 3 51875-0421-2 2

NDC 51875-042

Royce

ESTAZOLAM TABLETS

C IV

2 mg

Caution: Federal law prohibits dispensing without prescription.

1000 Tablets

Mfd. By: Royce Laboratories, Inc., Miami, FL 33014

Each tablet contains:
Estazolam ..... 2 mg

Usual Dosage:
See accompanying product literature.

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

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

Batch No.:

Exp. Date:

N 3 51875-0421-4 6

Each tablet contains:
Estazolam ..... 1 mg

Usual Dosage:
See accompanying product literature.

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

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

NDC 51875-0420-1

Royce TM

ESTAZOLAM TABLETS

IV

1 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 Tablets

Mfd. By: Royce Laboratories, Inc., Miami, FL 33014

1997

Batch No.:

Exp. Date:

N 3 51875-0420-1 6

Each tablet contains:
Estazolam ..... 1 mg

Usual Dosage:
See accompanying product literature.

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

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

NDC 51875-0420-2

Royce TM

ESTAZOLAM TABLETS

IV

1 mg

CAUTION: Federal law prohibits dispensing without prescription.

500 Tablets

Mfd. By: Royce Laboratories, Inc., Miami, FL 33014

1997

Batch No.:

Exp. Date:

N 3 51875-0420-2 3

Each tablet contains:
Estazolam ..... 1 mg

Usual Dosage:
See accompanying product literature.

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

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

NDC 51875-0420-4

Royce TM

ESTAZOLAM TABLETS

IV

1 mg

Caution: Federal law prohibits dispensing without prescription.

1000 Tablets

Mfd. By: Royce Laboratories, Inc., Miami, FL 33014

Batch No.:

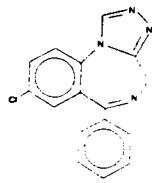
Exp. Date:

N 3 51875-0420-4 7

ESTAZOLAM TABLETS C IV

DESCRIPTION

Estazolam, a triazolobenzodiazepine derivative, is an oral hypnotic agent. Estazolam occurs as a fine, white, odorless powder that is soluble in alcohol and practically insoluble in water. The chemical name for estazolam is 8-chloro-6-phenyl-4H-s-triazolo[4,3-α][1,4]benzodiazepine. The molecular formula is $C_{16}H_{11}ClN_4$ and its molecular weight is 294.75. The structural formula is represented as follows:



Each tablet, for oral administration, contains 1 mg or 2 mg estazolam. In addition, each tablet contains the following inactive ingredients: docusate sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, sodium benzoate, sodium starch glycolate and stearic acid. The 2 mg tablets also contain FD&C Red #40 aluminum lake.

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 6.0 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 sites) 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 behavior 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.

sleep induction and maintenance, especially at the 2 mg dose, but only for sleep duration in subjective measures [illegible]

2

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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 0.6, 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 amount placebo-treated patients, were somnolence, hypokinesia, dizziness, and abnormal coordination.

Associated with Discontinuation of Treatment: Approximately 3% of 1277 patients who received estazolam in US 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. Event frequencies reported were not corrected for the occurrence of these events at baseline. The frequencies were obtained from data pooled across six studies: Estazolam, N=685; placebo, N=433. The prescriber should be aware 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 relative contribution of drug and nondrug factors to the incidence of side effects in the population studied.

INCIDENCE OF ADVERSE EXPERIENCE 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, 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-US 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 titrated or adjusted to patient

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-US 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, 1 mg are white, scored, diamond shaped compressed tablets, upper debossed 420 on left side of score and 1 on right side of score. The lower debossed with Royce Logo.

SIZE	ROYCE NDC NUMBER
Bottles of 100	51875-0420-1
Bottles of 500	51875-0420-2
Bottles of 1000	51875-0420-4

Estazolam Tablets, 2 mg, are dark pink, scored, diamond shaped compressed tablets, upper debossed 421 on left side of score and 2 on right side of score. The lower debossed with Royce Logo.

SIZE	ROYCE NDC NUMBER
Bottles of 100	51875-0421-1
Bottles of 500	51875-0421-2
Bottles of 1000	51875-0421-4

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

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

Caution - Federal law prohibits dispensing without prescription.

Royce Laboratories, Inc.
16600 NW 54 Avenue
Miami, FL 33014

Revised 10/96

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074818

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO 3

2. ANDA 74-818

3. NAME AND ADDRESS OF APPLICANT

Royce Laboratories, Inc.
Miami, FL 33014

4. LEGAL BASIS FOR SUBMISSION

505(j)

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 12/27/95; Amend 2/6/96; Labeling review 4/24/96; Bio Letter 5/17/96; NA Letter 6/19/96; Major Amendment 12/30/96; Labeling Review 1/17/97; NA Minor FAX 6/12/97; Minor Amend 6/18/97.

10. PHARMACOLOGICAL CATEGORY

Hypnotic

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM

White, scored diamond shaped tablets, upper side score debossed 420, on one side and 1 on the other. Lower side debossed with Royce Logo.

14. POTENCY

1 mg

Dark pink, scored diamond shaped tablets, upper side score debossed 421, on one side and 2 on the other. Lower side debossed with Royce Logo.	2 mg

15. CHEMICAL NAME AND STRUCTURE

Remains satisfactory (see review #1).

16. RECORDS AND REPORTS

N/A

17. COMMENTS

FPL found adequate on 7/10/97.

EER was found acceptable on 12/6/96.

Methods require validation. Method package was sent to the ATL-RL Lab on 5/28/97. To date the Laboratory has not returned their validated results and comments of the methods to us.

Bio data found adequate on 5/17/96. Bio also accepted Royce's dissolution test.

18. CONCLUSIONS AND RECOMMENDATIONS

Bio review acceptable.

EER acceptable.

Methods are being validation by ATL-RL.

Chemistry acceptable.

Approve with modified wording for method validation.

19. REVIEWER: _____ DATE COMPLETED:

Stephen Sherken July 15, 1997

cc: ANDA 74 -818
DIV FILE
Field Copy

Endorsements: 7/24/97

HFD-625/S.Sherken/7-15-97
HFD-625/M.Smela/7-17-97
X:\NEW\FIRMSNZ\ROYCE\LTRS&REV\7481[illegible].RV3 1/24/97
F/T by: bc/7-22-97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074818

BIOEQUIVALENCE REVIEW(S)

ANDA 74-818

Royce Laboratories, Inc.
Attention: Loren Gelber, Ph.D.
16600 NW 54th Avenue
Miami FL 33014

MAY 17 1996

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, 1 mg and 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 deaerated 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

MAY 10 1996

Estazolam Tablets, 1 mg & 2 mg
ANDA # 74-818
Reviewer: Hoainhon Nguyen
WP # 74818sdw.d95

Royce Laboratories
Miami, Florida
Submission Date:
December 27, 1995

Review of a Bioequivalence Study, Dissolution Data and a Waiver Request

I. Background:

Estazolam is a benzodiazepine, used as a hypnotic agent in the short-term management of insomnia, reportedly for periods of up to 12 weeks. Benzodiazepines generally are preferred to other hypnotics for management of insomnia because of their short- and intermediate-term efficacy and relative safety. The effects of the drug appear to be mediated through the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). Estazolam is practically insoluble in water.

Estazolam is rapidly and reportedly well absorbed from the GI tract following oral administration. The absolute bioavailability of estazolam and the effect of food on GI absorption of the drug have not been determined. Considerable interindividual variation in plasma concentrations attained with a given dose of estazolam has been reported. In a limited number of healthy adults, peak plasma estazolam concentrations averaging 99-103 ng/ml were achieved approximately 0.5-1.6 hours after a single, 2-mg oral dose of the drug as tablets or solution. In healthy men who received a single, 4-mg oral dose of the drug as tablets, peak plasma concentrations averaged 194 ng/ml at 1-3 hours after the dose. Peak plasma concentrations and elimination half-lives after single doses of estazolam are similar to those after multiple dosing, suggesting a linear, dose-independent pharmacokinetic profile of the drug.

Estazolam reportedly is 93% protein bound at concentrations ranging from 30-1000 ng/ml. Plasma concentrations of estazolam appear to decline in a biphasic manner, with a half-life in the initial distribution phase of approximately 17 minutes following single oral doses of the drug. The terminal elimination half-life averages 14-19 hours (range: 10-24 hours) following single or multiple doses.

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. Estazolam is rapidly and extensively metabolized in the liver. Plasma concentrations of the drug's principal metabolites, 4-hydroxyestazolam and 1-oxoestazolam, are low or undetectable; these metabolites have little to no pharmacologic activity in humans. Estazolam is excreted in both urine and feces, principally as inactive metabolites. Unchanged drug accounts for less than 5% of a dose excreted in urine. Following oral administration of radiolabeled estazolam in healthy adults, approximately 91% of a dose was excreted in urine (87%) and feces (4%) over a 5-day period.

Most commonly observed adverse events associated with estazolam are somnolence, hypokinesia, dizziness, and abnormal coordination.

Estazolam is available commercially as ProSom^{R} oral tablets, 1 mg and 2 mg, manufactured by Abbott Laboratories. The effect of food has not been studied and the drug is given at bedtime.

The firm has submitted the results of a fasting, single-dose bioequivalence study comparing its Estazolam tablets, 2 mg, with Abbott's ProSom^{R} tablets, 2 mg. The firm has also submitted comparative dissolution data for the 2 mg and 1 mg strengths of the test and reference products in support of a request for waiver of in-vivo bioequivalence requirements for the lower strength of the test product.

Note: Currently, the Division of Bioequivalence does not require a food study for approval of an estazolam tablet product.

II. Bioequivalence Study: (Protocol No. 10936, Study No. 047-22-10936)

Study Objective:

The purpose of this study is to evaluate the bioequivalency of Royce's estazolam tablets, 2 mg, and Abbott's ProSom^{R} Tablets, 2 mg, in a fasting single dose, two-treatment, two-period crossover study design.

Study Investigators and Facilities:

The study was conducted at between September 15, 1995 and October 1, 1995. The principal investigator was Plasma samples were assayed by under the supervision of between October 5, 1995 and October 24, 1995.

Demographics:

Twenty-eight normal, healthy male volunteers between 19-47 years of age, and within 15% of their ideal weight according to the Metropolitan Life Insurance Company Bulletin, 1983, participated in a two-treatment, two-period, randomized crossover study. The subjects were selected on the basis of their acceptable medical history, physical examination and clinical laboratory tests. The subjects' weight and height ranged 120 - 198 lbs and 65 - 75 in., respectively.

Inclusion criteria:

Subjects especially did not have any history of: psychiatric, serious cardiovascular, neurological, hepatic, renal, hematopoietic, gastrointestinal diseases; or ongoing infectious diseases, alcohol or drug abuse; or known allergy to estazolam or to any benzodiazepine.

Restrictions:

They were free of all medications at least 7 days (for OTC medications) to 14 days (for prescription) prior to each study period and allowed no concomitant medications during the study sessions. No alcohol consumption was allowed 48 hours prior to and throughout each study period. No caffeine was allowed for 12 hours prior to and throughout each study period. The subjects fasted for 10 hours prior to and 5 hours after each drug administration. The washout duration between the two phases was two weeks. Duration of confinement was 12 hours pre-dose to approximately 24 hours post-dose.

Treatments and Sampling:

The two treatments consisted of a single 2 mg dose of either the test product or reference product taken orally with 240 ml of water.

Test Product: Royce's Estazolam Tablets, 2 mg, lot # MG-1453 (Batch size of units, potency of 100.1% (RSD=1.4%)).

Reference product: Abbott's ProSom^{R} Tablets, 2 mg, lot # 95-426-AA-21 (Potency of 99.9% (RSD=7.3%)).

Blood samples were collected at predose, 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48 and 72 hours following drug administration. Blood samples were centrifuged and the plasma was separated and immediately stored at -20^{0}C until analysis.

Assay Methodology:

Pharmacokinetic Results:

AUC(0-T) was calculated using the trapezoidal method. AUC(0-Infinity) was calculated by : AUC(0-Infinity) = AUC(0-T) + [last measured concentration/ KEL].

CMAX and TMAX were observed values of the peak plasma concentration and time to peak plasma concentration, respectively. KEL and T1/2 were calculated from the terminal portion of the log concentration versus time curve.

Statistical Analyses:

Analysis of variance and F-test were used to determine statistically significant (p less than 0.05) differences between treatments, sequences of treatment, subjects within sequence, and days of administration for the above pharmacokinetic parameters as well as for the plasma concentrations at each sampling time. The 90% confidence intervals for AUC's, CMAX, lnAUC's and lnCMAX were calculated, based on least squares means, using the two, one-sided t-test.

Results:

Twenty-six of twenty-eight enrolled volunteers completed the clinical portion of the study. Subject # 18 withdrew voluntarily from the study after the first period. Subject # 21 withdrew from the study because of a family emergency. The statistical analysis was performed using 26 unbalanced data sets (12 subjects with sequence AB, and 14 with BA).

There was no significant difference (alpha=0.05) between treatments for AUC (0-T), AUC (0-Infinity), CMAX, lnAUC(0-T), lnAUC(0-Infinity), lnCMAX and TMAX. Note: Plasma concentration data were spot-checked. ANOVA by SAS-PROC GLM for AUCT, AUCI, CMAX, lnAUCT, lnAUCI and lnCMAX, and 90% confidence interval calculation for lnAUCT, lnAUCI and lnCMAX were also checked. The results were verified with checking.

The results of the study are summarized in the tables below:

Table I

Estazolam Comparative Pharmacokinetic Parameters

Dose = 2 mg; n = 26

Parameters	Royce's Mean (CV%)	ProSom® Mean (CV%)	90% C.I.	Ratio T/R
AUC (0-T) ng.hr/ml	1869*	1907*	[0.94;1.03]	0.98
AUC (0-Inf) ng.hr/ml	2029*	2085*	[0.93;1.02]	0.97
CMAX(ng/ml)	92.61*	93.08*	[0.95;1.04]	0.99
TMAX (hrs)	1.418(80)	1.418(81)		
KEL (1/hrs)	0.043(22)	0.041(22)		
T1/2 (hrs)	17.06(24)	17.49(22)		

*Least Squares Geometric Means

Table II

Comparative Mean Plasma Levels of Estazolam

Dose = 2 mg; n = 26

ng/ml(CV%)

Hour	Royce's	ProSom^{R}
0	0	0
0.33	30.51(63)	36.56(88)
0.67	77.89(38)	80.15(32)
1.00	81.68(32)	86.81(21)
1.33	81.74(26)	85.27(19)
1.67	83.26(21)	86.18(18)
2.00	80.63(17)	83.06(17)
2.50	76.86(20)	81.64(18)
3.00	72.65(15)	75.95(18)
4.00	69.01(19)	71.23(19)
5.00	65.56(18)	66.72(19)
6.00	70.56(19)	71.52(19)
8.00	68.95(20)	68.49(15)
10.00	58.02(22)	57.87(20)
12.00	53.86(22)	53.85(19)
16.00	43.45(25)	44.28(23)
24.00	30.93(32)	31.10(32)
36.00	19.16(38)	19.06(37)
48.00	11.87(47)	12.08(45)
72.00	4.17(89)	4.21(84)
AUC(0-T)ng.hr/ml	1937(28)	1961(26)
AUC(0-Inf)ng.hr/ml	2103(28)	2142(25)
CMAX	94.18(19)	94.72(20)

Adverse Effects:

Twenty-three subjects reported forty-two adverse events. Forty-one possibly drug-related events were mild in severity; twenty-one events occured under test treatment and twenty under reference treatment. Drowsiness and irritability were the two most frequently reported events.

III. Dissolution Testing:

Drug (Generic Name): Estazolam Tablets
Dose Strength: 1 mg and 2 mg
Submission Date: December 27, 1995

Firm: Royce Laboratories
ANDA # 74-818

Table - In-Vitro Dissolution Testing

I. Conditions for Dissolution Testing:

USP XXI Basket ____ Paddle X RPM 50 No. Units Tested: 12

Medium: Deaerated Water Volume: 900 ml

Reference Drug: (Manuf.) ProSom® Tablets (Abbott)

Assay Methodology: _____

II. Results of In-Vitro Dissolution Testing:

Sampling Times (Min)	Test Product Lot # MG-1452 Strength (mg) 1 Mean % Dissolved	Range	(CV)	Reference Product Lot # 93-302-AA-21 Strength (mg) 1 Mean % Dissolved	Range	(CV)
5	77.7		(9.0%)	92.6		(2.9%)
10	98.0		(2.6%)	98.4		(2.1%)
20	102.2		(1.6%)	100.8		(1.8%)
30	102.3		(1.1%)	101.5		(1.7%)
45	102.3		(1.5%)	101.4		(2.2%)

Sampling Times (Min)	Test Product Lot # MG-1453 Strength (mg) 2 Mean % Dissolved	Range	(CV)	Reference Product Lot # 95-426-AA-21 Strength (mg) 2 Mean % Dissolved	Range	(CV)
5	75.4		(7.2%)	93.2		(9.7 %)
10	96.9		(5.3%)	94.4		(4.2 %)
20	101.2		(2.7%)	99.2		(3.3%)
30	101.0		(2.3%)	100.6		(2.9%)
45	101.2		(2.0%)	101.9		(2.9%)

Current Specification:

NLT in 30 min

IV. Comments:

1. The single-dose, fasting bioequivalence study conducted by Royce Laboratories on the test product, Estazolam Tablets, 2 mg, lot # MG-1453, comparing it with the reference product, ProSom^{R} Tablets, 2 mg, lot # 95-426-AA-21, demonstrates that the test product is equivalent to the reference product in their rate and extent of absorption as measured by lnCMAX, lnAUC(0-T) and lnAUC(0-Infinity) of estazolam.

2. The in vitro dissolution data for the 2 mg and 1 mg strengths of the test product are acceptable.

3. Comparative formulations given for the 1 mg and 2 mg strengths of the test product show that the 1 mg strength is proportionally similar to the 2 mg strength. (See attachment)

V. Recommendations:

1. The single-dose, fasting bioequivalence study conducted by Royce Laboratories on the test product, Estazolam Tablets, 2 mg, lot # MG-1453, comparing it with the reference product, ProSom^{R} Tablets, 2 mg, lot # 95-426-AA-21, has been found acceptable by the Division of Bioequivalence. The study demonstrates that the test product is bioequivalent to the reference product under fasting conditions.

2. The in-vitro dissolution testing conducted by Royce Laboratories on its Estazolam Tablets, 2 mg and 1 mg, has been found acceptable.

The dissolution testing should be incorporated by the firm into its manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml of deaerated water at 37C using USP XXIII 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.

3. The firm has demonstrated that the formulation of its Estazolam Tablets, 1 mg, is proportionally similar to the 2 mg strength that underwent acceptable in vivo bioequivalence testing. The waiver of in vivo bioequivalence study requirements for the 1 mg tablets is granted. The firm's Estazolam Tablets, 1 mg, is therefore deemed

bioequivalent to ProSom[K] Tablets, 1 mg, manufactured by Abbott.

5/8/96

Hoainhon Nguyen
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG 5/7/96

Concur: _____ Date: 5/10/96
Keith Chan, Ph.D.
Director, Division of Bioequivalence

cc: ANDA # 74-818 (original, duplicate), HFD-630(OGD), HFD-600(Hare), HFD-652(Huang, Nguyen), HFD-344(CViswanathan), Drug File, Division File

Hnguyen/04-09-96/WP #74818sdw.d95

Attachments: 2 pages

Formulation of Royce Laboratories'
Estazolam Tablets,
1 mg, and 2 mg

Ingredients (mg)	Estazolam Tablets 1 mg	Estazolam Tablets 2 mg
Estazolam	1.0	2.0
Microcrystalline Cellulose, NF		
Docusate Sodium/Sodium Benzoate		
Sodium Starch Glycolate NF		
FD&C Red #40		
Lactose Monohydrate NF		
Stearic Acid, NF		
Magnesium Stearate, NF		
Total Weight (mg)	150.0	150.0

Figure 1: Mean Estazolam Plasma Levels

#047 – 22 – 10936

N = 26