CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 17-105/S-059/S-062

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 17-105/S-059/062

Abbott Laboratories
Attention: Steven Townsend
Associate Director, PPD Regulatory Affairs
200 Abbott Park Rd., D-491, AP30-1E
Abbott Park, IL 60064-6157

Dear Mr. Townsend:

Please refer to your supplemental new drug applications dated April 16, 1987 (S-059) and September 10-1987 (S-062), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tranxene (clorazepate dipotassium) dosages.

We acknowledge receipt of your amendments dated December 23, 1987, and June 7, 1994, submitted to supplemental application 062.

These "Changes Being Effected" supplemental new drug applications provide for the following changes to product labeling:

S-059
The placement of a revision date, a substance symbol, and the use of the "T-Tab" symbol in labeling.

S-062
Revisions in labeling to incorporate additional information on withdrawal problems associated with benzodiazepines, additional pharmacokinetic information, and editorial revisions. We note that this supplement responded to an Agency letter dated July 8, 1987, and February 17, 1988, requesting revisions to product labeling. We additionally note that you incorporated our requested revisions verbatim.

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted final printed labeling (package insert submitted June 7, 1994/Label Code 03-4490-R13). Accordingly, these supplemental applications are approved effective on the date of this letter.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Mr. Paul David, R.Ph., Senior Regulatory Project Manager, at (301) 594-5530.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Russell Katz
2/7/02 08:20:22 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 17-105/S-059/S-062

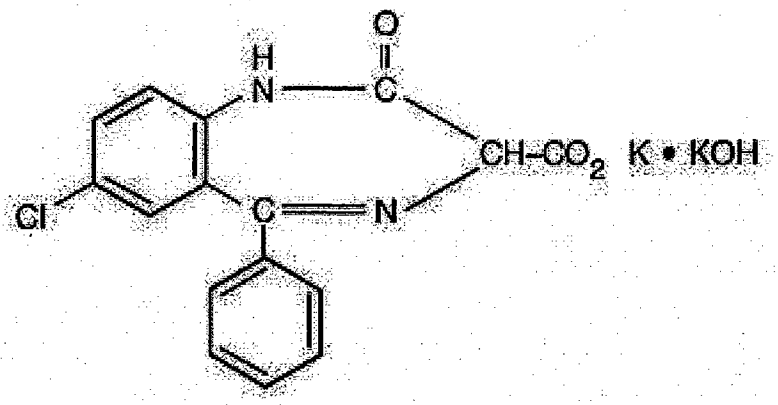
FINAL PRINTED LABELING

New: December, 2002

TRANXENE® T-TAB Tablets (Nos. 301,302,303)
CLORAZEPATE DIPOTASSIUM
TRANXENE®-SD &
TRANXENE®-SD HALF STRENGTH (Nos. 405, 404)
CLORAZEPATE DIPOTASSIUM
SINGLE DOSE TABLETS

DESCRIPTION

Chemically, TRANXENE is a benzodiazepine. The empirical formula is $C_{16}H_{11}ClK_2N_2O_4$; the molecular weight is 408.92; and the structural formula may be represented as follows:



The compound occurs as a fine, light yellow, practically odorless powder. It is insoluble in the common organic solvents, but very soluble in water. Aqueous solutions are unstable, clear, light yellow, and alkaline.

TRANXENE T-TAB tablets contain either 3.75 mg, 7.5 mg or 15 mg of clorazepate dipotassium for oral administration. TRANXENE-SD and TRANXENE-SD HALF STRENGTH tablets contain 22.5 mg and 11.25 mg of clorazepate dipotassium respectively. TRANXENE-SD and TRANXENE-SD HALF STRENGTH tablets gradually release clorazepate and are designed for once-a-day administration in patients already stabilized on TRANXENE T-TAB tablets.

Inactive ingredients for TRANXENE T-TAB® Tablets: Colloidal silicon dioxide, FD&C Blue No. 2 (3.75 mg only), FD&C Yellow No. 6 (7.5 mg only), FD&C Red No. 3 (15 mg only), magnesium oxide, magnesium stearate, microcrystalline cellulose, potassium carbonate, potassium chloride, and talc. Inactive ingredients for TRANXENE-SD and TRANXENE-SD HALF STRENGTH Tablets: Castor oil wax, FD&C Blue No. 2 (SD Half Strength, 11.25 mg only), iron oxide (SD, 22.5 mg only), lactose, magnesium oxide, magnesium stearate, potassium carbonate, potassium chloride, and talc.

CLINICAL PHARMACOLOGY

Pharmacologically, clorazepate dipotassium has the characteristics of the benzodiazepines. It has depressant effects on the central nervous system. The primary

metabolite, nordiazepam, quickly appears in the blood stream. The serum half-life is about 2 days. The drug is metabolized in the liver and excreted primarily in the urine.

Studies in healthy men have shown that clorazepate dipotassium has depressant effects on the central nervous system. Prolonged administration of single daily doses as high as 120 mg was without toxic effects. Abrupt cessation of high doses was followed in some patients by nervousness, insomnia, irritability, diarrhea, muscle aches, or memory impairment.

Since orally administered clorazepate dipotassium is rapidly decarboxylated to form nordiazepam, there is essentially no circulating parent drug. Nordiazepam, the primary metabolite, quickly appears in the blood and is eliminated from the plasma with an apparent half-life of about 40 to 50 hours. Plasma levels of nordiazepam increase proportionally with TRANXENE dose and show moderate accumulation with repeated administration. The protein binding of nordiazepam in plasma is high (97-98%).

Within 10 days after oral administration of a 15 mg (50μCi) dose of ^{14}C-TRANXENE to two volunteers, 62-67% of the radioactivity was excreted in the urine and 15-19% was eliminated in the feces. Both subjects were still excreting measurable amounts of radioactivity in the urine (about 1% of the ^{14}C-dose) on day ten.

Nordiazepam is further metabolized by hydroxylation. The major urinary metabolite is conjugated oxazepam (3-hydroxynordiazepam), and smaller amounts of conjugated p-hydroxynordiazepam and nordiazepam are also found in the urine.

INDICATIONS AND USAGE

TRANXENE is indicated for the management of anxiety disorders or for the short-term relief of the symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.

TRANXENE tablets are indicated as adjunctive therapy in the management of partial seizures.

The effectiveness of TRANXENE tablets in long-term management of anxiety, that is, more than 4 months, has not been assessed by systematic clinical studies. Long-term studies in epileptic patients, however, have shown continued therapeutic activity. The physician should reassess periodically the usefulness of the drug for the individual patient.

TRANXENE tablets are indicated for the symptomatic relief of acute alcohol withdrawal.

CONTRAINDICATIONS

TRANXENE tablets are contraindicated in patients with a known hypersensitivity to the drug and in those with acute narrow angle glaucoma.

WARNINGS

TRANXENE tablets are not recommended for use in depressive neuroses or in psychotic reactions.

Patients taking TRANXENE tablets should be cautioned against engaging in hazardous occupations requiring mental alertness, such as operating dangerous machinery including motor vehicles.

Since TRANXENE has a central nervous system depressant effect, patients should be advised against the simultaneous use of other CNS-depressant drugs, and cautioned that the effects of alcohol may be increased.

Because of the lack of sufficient clinical experience, TRANXENE tablets are not recommended for use in patients less than 9 years of age.

Physical and Psychological Dependence:
Withdrawal symptoms (similar in character to those noted with barbiturates and alcohol) have occurred following abrupt discontinuance of clorazepate. Withdrawal symptoms associated with the abrupt discontinuation of benzodiazepines have included convulsions, delirium, tremor, abdominal and muscle cramps, vomiting, sweating, nervousness, insomnia, irritability, diarrhea, and memory impairment. The more severe withdrawal symptoms have usually been limited to those patients who had received excessive doses over an extended period of time. Generally milder withdrawal symptoms have been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months. Consequently, after extended therapy, abrupt discontinuation of clorazepate should generally be avoided and a gradual dosage tapering schedule followed.

Caution should be observed in patients who are considered to have a psychological potential for drug dependence.

Evidence of drug dependence has been observed in dogs and rabbits which was characterized by convulsive seizures when the drug was abruptly withdrawn or the dose was reduced; the syndrome in dogs could be abolished by administration of clorazepate.

Usage in Pregnancy:
An increased risk of congenital malformations associated with the use of minor tranquilizers (chlordiazepoxide, diazepam, and meprobamate) during the first trimester of pregnancy has been suggested in several studies. Clorazepate dipotassium, a benzodiazepine derivative, has not been studied adequately to determine whether it, too, may be associated with an increased risk of fetal abnormality. Because use of these drugs is rarely a matter of urgency, their use during this period should almost always be avoided. The possibility that a woman of childbearing potential may be pregnant at the time of institution of therapy should be considered. Patients should be advised that if they become pregnant during therapy or intend to become pregnant they should communicate with their physician about the desirability of discontinuing the drug.

Usage during Lactation:
TRANXENE tablets should not be given to nursing mothers since it has been reported that nordiazepam is excreted in human breast milk.

PRECAUTIONS

In those patients in which a degree of depression accompanies the anxiety, suicidal tendencies may be present and protective measures may be required. The least amount of drug that is feasible should be available to the patient.

Patients taking TRANXENE tablets for prolonged periods should have blood counts and liver function tests periodically. The usual precautions in treating patients with impaired renal or hepatic function should also be observed.

In elderly or debilitated patients, the initial dose should be small, and increments should be made gradually, in accordance with the response of the patient, to preclude ataxia or excessive sedation.

Information for Patients:
To assure the safe and effective use of benzodiazepines, patients should be informed that, since benzodiazepines may produce psychological and physical dependence, it is essential that they consult with their physician before either increasing the dose or abruptly discontinuing this drug.
Pediatric Use: See **WARNINGS**.
Geriatric Use: Clinical studies of Tranxene were not adequate to determine whether subjects aged 65 and over respond differently than younger subjects. Elderly or debilitated patients may be especially sensitive to the effects of all benzodiazepines, including Tranxene. In general, elderly or debilitated patients should be started on lower doses of Tranxene and observed closely, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Dose adjustments should also be made slowly, and with more caution in this patient population (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS

The side effect most frequently reported was drowsiness. Less commonly reported (in descending order of occurrence) were: dizziness, various gastrointestinal complaints, nervousness, blurred vision, dry mouth, headache, and mental confusion. Other side effects included insomnia, transient skin rashes, fatigue, ataxia, genitourinary complaints, irritability, diplopia, depression, tremor, and slurred speech.

There have been reports of abnormal liver and kidney function tests and of decrease in hematocrit.

Decrease in systolic blood pressure has been observed.

DOSAGE AND ADMINISTRATION

For the symptomatic relief of anxiety:
TRANXENE T-TAB® tablets are administered orally in divided doses. The usual daily dose is 30 mg. The dose should be adjusted gradually within the range of 15 to 60 mg daily in accordance with the response of the patient. In elderly or debilitated patients it is advisable to initiate treatment at a daily dose of 7.5 to 15 mg.

TRANXENE tablets may also be administered in a single dose daily at bedtime; the recommended initial dose is 15 mg. After the initial dose, the response of the patient may require adjustment of subsequent dosage. Lower doses may be indicated in the elderly patient. Drowsiness may occur at the initiation of treatment and with dosage increment.

TRANXENE-SD (22.5 mg) tablets may be administered as a single dose every 24 hours. This tablet is intended as an alternate dosage form for the convenience of patients

stabilized on a dose of 7.5 mg tablets three times a day. TRANXENE-SD tablets should not be used to initiate therapy.

TRANXENE-SD HALF STRENGTH (11.25 mg) tablets may be administered as a single dose every 24 hours. This tablet is intended as an alternate dosage form for the convenience of patients stabilized on a dose of 3.75 mg tablets three times a day. TRANXENE-SD HALF STRENGTH should not be used to initiate therapy.

For the symptomatic relief of acute alcohol withdrawal:

The following dosage schedule is recommended:

1st 24 hours (Day 1)	30 mg initially; followed by 30 to 60 mg in divided doses
2nd 24 hours (Day 2)	45 to 90 mg in divided doses
3rd 24 hours (Day 3)	22.5 to 45 mg in divided doses
Day 4	15 to 30 mg in divided doses

Thereafter, gradually reduce the daily dose to 7.5 to 15 mg. Discontinue drug therapy as soon as patient's condition is stable.

The maximum recommended total daily dose is 90 mg. Avoid excessive reductions in the total amount of drug administered on successive days.

As an Adjunct to Antiepileptic Drugs:

In order to minimize drowsiness, the recommended initial dosages and dosage increments should not be exceeded.

Adults: The maximum recommended initial dose in patients over 12 years old is 7.5 mg three times a day. Dosage should be increased by no more than 7.5 mg every week and should not exceed 90 mg/day.

Children (9-12 years): The maximum recommended initial dose is 7.5 mg two times a day. Dosage should be increased by no more than 7.5 mg every week and should not exceed 60 mg/day.

DRUG INTERACTIONS

If TRANXENE is to be combined with other drugs acting on the central nervous system, careful consideration should be given to the pharmacology of the agents to be employed. Animal experience indicates that clorazepate dipotassium prolongs the sleeping time after hexobarbital or after ethyl alcohol, increases the inhibitory effects of chlorpromazine, but does not exhibit monoamine oxidase inhibition. Clinical studies have shown increased sedation with concurrent hypnotic medications. The actions of the benzodiazepines may be potentiated by barbiturates, narcotics, phenothiazines, monoamine oxidase inhibitors or other antidepressants.

If TRANXENE tablets are used to treat anxiety associated with somatic disease states, careful attention must be paid to possible drug interaction with concomitant medication.

In bioavailability studies with normal subjects, the concurrent administration of antacids at therapeutic levels did not significantly influence the bioavailability of TRANXENE tablets.

OVERDOSAGE

Overdosage is usually manifested by varying degrees of CNS depression ranging from slight sedation to coma. As in the management of overdosage with any drug, it should be borne in mind that multiple agents may have been taken.

The treatment of overdosage should consist of the general measures employed in the management of overdosage of any CNS depressant. Gastric evacuation either by the induction of emesis, lavage, or both, should be performed immediately. General supportive care, including frequent monitoring of the vital signs and close observation of the patient, is indicated. Hypotension, though rarely reported, may occur with large overdoses. In such cases the use of agents such as Levophed® Bitartrate (norepinephrine bitartrate injection, USP) or Aramine® Injection (metaraminol bitartrate injection, USP) should be considered.

While reports indicate that individuals have survived overdoses of clorazepate dipotassium as high as 450 to 675 mg, these doses are not necessarily an accurate indication of the amount of drug absorbed since the time interval between ingestion and the institution of treatment was not always known. Sedation in varying degrees was the most common physiological manifestation of clorazepate dipotassium overdosage. Deep coma when it occurred was usually associated with the ingestion of other drugs in addition to clorazepate dipotassium.

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.

ANIMAL PHARMACOLOGY AND TOXICOLOGY

Studies in rats and monkeys have shown a substantial difference between doses producing tranquilizing, sedative and toxic effects. In rats, conditioned avoidance response was inhibited at an oral dose of 10 mg/kg; sedation was induced at 32 mg/kg; the LD_{50} was 1320 mg/kg. In monkeys aggressive behavior was reduced at an oral dose of 0.25 mg/kg; sedation (ataxia) was induced at 7.5 mg/kg; the LD_{50} could not be determined because of the emetic effect of large doses, but the LD_{50} exceeds 1600 mg/kg.

Twenty-four dogs were given clorazepate dipotassium orally in a 22-month toxicity study; doses up to 75 mg/kg were given. Drug-related changes occurred in the liver; weight was increased and cholestasis with minimal hepatocellular damage was found, but lobular architecture remained well preserved.

Eighteen rhesus monkeys were given oral doses of clorazepate dipotassium from 3 to 36 mg/kg daily for 52 weeks. All treated animals remained similar to control

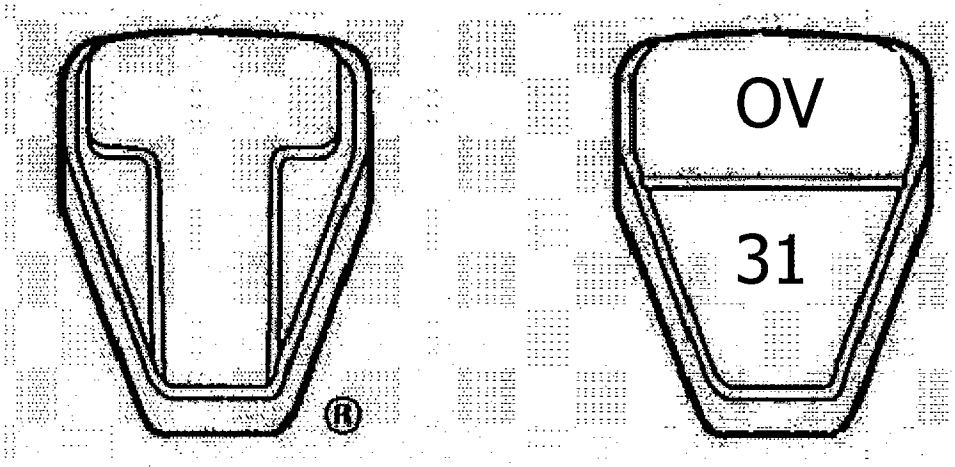
animals. Although total leucocyte count remained within normal limits it tended to fall in the female animals on the highest doses.

Examination of all organs revealed no alterations attributable to clorazepate dipotassium. There was no damage to liver function or structure.

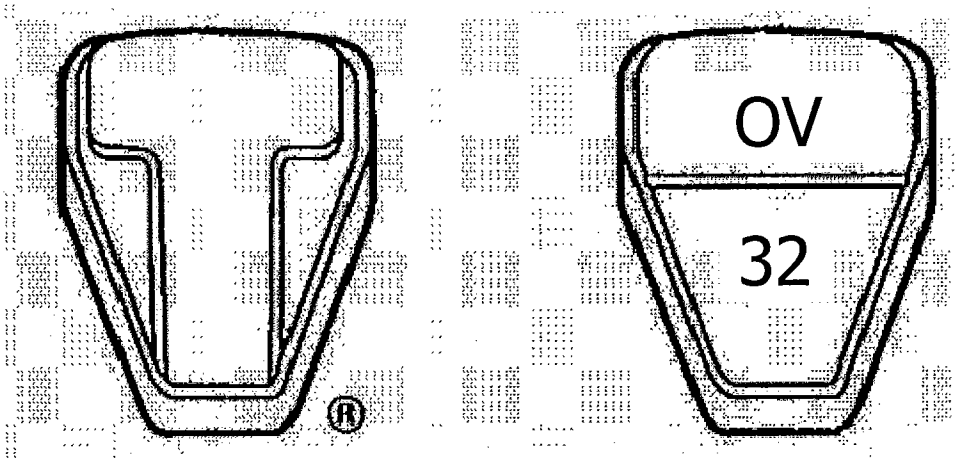
Reproduction Studies:
Standard fertility, reproduction, and teratology studies were conducted in rats and rabbits. Oral doses in rats up to 150 mg/kg and in rabbits up to 15 mg/kg produced no abnormalities in the fetuses. TRANXENE did not alter the fertility indices or reproductive capacity of adult animals. As expected, the sedative effect of high doses interfered with care of the young by their mothers (see *Usage in Pregnancy*).

HOW SUPPLIED

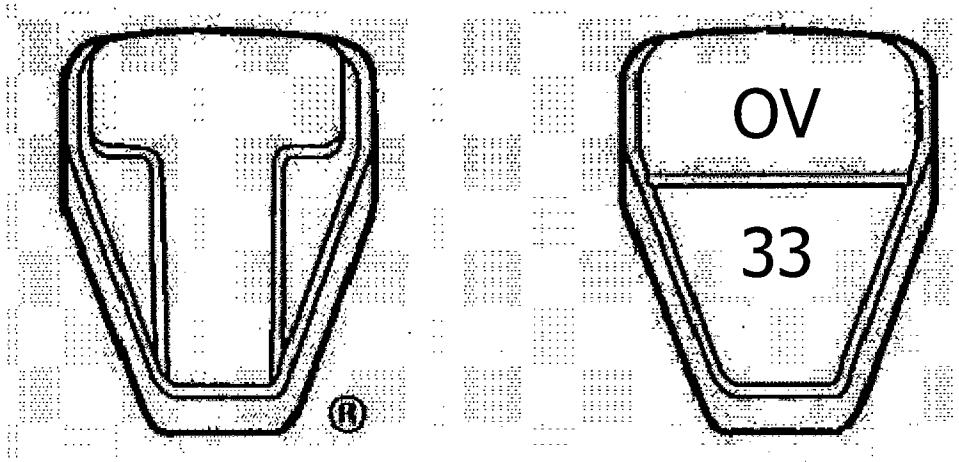
TRANXENE® 3.75 mg, scored T-TAB tablets are supplied as blue-colored tablets bearing the letters OV, the distinctive T shape and a two-digit designation, 31.
Bottles of 100 ..... **(NDC 67386-301-01)**



7.5 mg scored T-TAB tablets are supplied as peach-colored tablets bearing the letters OV, the distinctive T shape and a two-digit designation, 32.
Bottles of 100 ..... **(NDC 67386-302-01)**
Bottles of 500 ..... **(NDC 67386-302-05)**



15 mg scored T-TAB tablets are supplied as lavender-colored tablets bearing the letters OV, the distinctive T shape and a two-digit designation, 33.
Bottles of 100 ..... (NDC 67386-303-01)



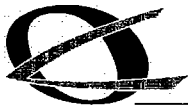
TRANXENE®-SD 22.5 mg single dose tablets are supplied as tan-colored tablets bearing the letters OV and a two-digit designation, 45.
Bottles of 100 ..... **(NDC 67386-405-01)**

TRANXENE®-SD HALF STRENGTH 11.25 mg single dose tablets are supplied as blue-colored tablets bearing the letters OV and a two-digit designation, 44.
Bottles of 100 ..... **(NDC 67386-404-01)**

Protect from moisture. Keep bottle tightly closed.
Store below 77°F (25°C).
Dispense in a USP tight, light-resistant container.

T-TAB, tablet appearance and shape are registered trademarks of Ovation Pharmaceuticals. U.S. Design Pat. No. D-300,879
®Registered trademark of Ovation Pharmaceuticals, Inc.

Manufactured by Abbott Laboratories, North Chicago, Illinois, 60064 for:



OVATION PHARMACEUTICALS, INC.
Deerfield, Illinois 60015 U.S.A.

December 2002

03-4490-R13-Rev. March, 1994

TRANXENE® CLORAZEPATE DIPOTASSIUM

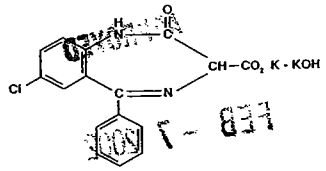
T-TAB® Tablets (Nos. 4389, 4390, 4391)

TRANXENE®-SD™ & TRANXENE®-SD™ HALF STRENGTH

Tablets (Nos. 2997, 2699)

DESCRIPTION

Chemically, TRANXENE (clorazepate dipotassium) is a benzodiazepine. The empirical formula is $C_{16}H_{11}ClK_2N_2O_4$; the molecular weight is 408.92; and the structural formula may be represented as follows:



The compound occurs as a fine, light yellow, practically odorless powder. It is insoluble in the common organic solvents, but very soluble in water. Aqueous solutions are unstable, clear, light yellow, and alkaline.

TRANXENE T-TAB tablets contain either 3.75 mg, 7.5 mg or 15 mg of clorazepate dipotassium for oral administration. TRANXENE-SD and TRANXENE-SD HALF STRENGTH tablets contain 22.5 mg and 11.25 mg of clorazepate dipotassium respectively. TRANXENE-SD and TRANXENE-SD HALF STRENGTH tablets gradually release clorazepate and are designed for once-a-day administration in patients already stabilized on TRANXENE T-TAB tablets.

Inactive ingredients for TRANXENE T-TAB® Tablets: Colloidal silicon dioxide, FD&C Blue No. 2 (3.75 mg only), FD&C Yellow No. 6 (7.5 mg only), FD&C Red No. 3 (15 mg only), magnesium oxide, magnesium stearate, microcrystalline cellulose, potassium carbonate, potassium chloride, and talc. Inactive ingredients for TRANXENE-SD and TRANXENE-SD HALF STRENGTH Tablets: Castor oil wax, FD&C Blue No. 2 (SD Half Strength, 11.25 mg only), iron oxide (SD, 22.5 mg only), lactose, magnesium oxide, magnesium stearate, potassium carbonate, potassium chloride, and talc.

CLINICAL PHARMACOLOGY

Pharmacologically, clorazepate dipotassium has the characteristics of the benzodiazepines. It has depressant effects on the central nervous system. The primary metabolite, nordiazepam, quickly appears in the blood stream. The serum half-life is about 2 days. The drug is metabolized in the liver and excreted primarily in the urine.

Studies in healthy men have shown that clorazepate dipotassium has depressant effects on the central nervous system. Prolonged administration of single daily doses as high as 120 mg was without toxic effects. Abrupt cessation of high doses was followed in some patients by nervousness, insomnia, irritability, diarrhea, muscle aches, or memory impairment.

Since orally administered clorazepate dipotassium is rapidly decarboxylated to form nordiazepam, there is essentially no circulating parent drug. Nordiazepam, the primary metabolite, quickly appears in the blood and is eliminated from the plasma with an apparent half-life of about 40 to 50 hours. Plasma levels of nordiazepam increase proportionally with TRANXENE dose and show moderate accumulation with repeated administration. The protein binding of nordiazepam in plasma is high (97-98%).

Within 10 days after oral administration of a 15 mg (50μCi) dose of ^{14}C-TRANXENE to two volunteers, 62-67% of the radioactivity was excreted in the urine and 15-19% was eliminated in the feces. Both subjects were still excreting measurable amounts of radioactivity in the urine (about 1% of the ^{14}C-dose) on day ten.

Nordiazepam is further metabolized by hydroxylation. The major urinary metabolite is conjugated oxazepam (3-hydroxynordiazepam), and smaller amounts of conjugated p-hydroxynordiazepam and nordiazepam are also found in the urine.

INDICATIONS AND USAGE

TRANXENE (clorazepate dipotassium) is indicated for the management of anxiety disorders or for the short-term relief of the symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.

TRANXENE tablets are indicated as adjunctive therapy in the management of partial seizures.

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TRANXENE tablets are indicated as adjunctive therapy in the management of partial seizures.

The effectiveness of TRANXENE tablets in long-term management of anxiety, that is, more than 4 months, has not been assessed by systematic clinical studies. Long-term studies in epileptic patients, however, have shown continued therapeutic activity. The physician should reassess periodically the usefulness of the drug for the individual patient.

TRANXENE tablets are indicated for the symptomatic relief of acute alcohol withdrawal.

CONTRAINDICATIONS

TRANXENE tablets are contraindicated in patients with a known hypersensitivity to the drug and in those with acute narrow angle glaucoma.

WARNINGS

TRANXENE tablets are not recommended for use in depressive neuroses or in psychotic reactions.

Patients taking TRANXENE tablets should be cautioned against engaging in hazardous occupations requiring mental alertness, such as operating dangerous machinery including motor vehicles.

Since TRANXENE (clorazepate dipotassium) has a central nervous system depressant effect, patients should be advised against the simultaneous use of other CNS-depressant drugs, and cautioned that the effects of alcohol may be increased.

Because of the lack of sufficient clinical experience, TRANXENE tablets are not recommended for use in patients less than 9 years of age.

Physical and Psychological Dependence:

Withdrawal symptoms (similar in character to those noted with barbiturates and alcohol) have occurred following abrupt discontinuance of clorazepate. Withdrawal symptoms associated with the abrupt discontinuation of benzodiazepines have included convulsions, delirium, tremor, abdominal and muscle cramps, vomiting, sweating, nervousness, insomnia, irritability, diarrhea, and memory impairment. The more severe withdrawal symptoms have usually been limited to those patients who had received excessive doses over an extended period of time. Generally milder withdrawal symptoms have been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months. Consequently, after extended therapy, abrupt discontinuation of clorazepate should generally be avoided and a gradual dosage tapering schedule followed.

Caution should be observed in patients who are considered to have a psychological potential for drug dependence.

Evidence of drug dependence has been observed in dogs and rabbits which was characterized by convulsive seizures when the drug was abruptly withdrawn or the dose was reduced; the syndrome in dogs could be abolished by administration of clorazepate.

Usage in Pregnancy:

An increased risk of congenital malformations associated with the use of minor tranquilizers (chlordiazepoxide, diazepam, and meprobamate) during the first trimester of pregnancy has been suggested in several studies. Clorazepate dipotassium, a benzodiazepine derivative, has not been studied adequately to determine whether it, too, may be associated with an increased risk of fetal abnormality. Because use of these drugs is rarely a matter of urgency, their use during this period should almost always be avoided. The possibility that a woman of childbearing potential may be pregnant at the time of institution of therapy should be considered. Patients should be advised that if they become pregnant during therapy or intend to become pregnant they should communicate with their physician about the desirability of discontinuing the drug.

Usage during Lactation:

TRANXENE tablets should not be given to nursing mothers since it has been reported that nordiazepam is excreted in human breast milk.

PRECAUTIONS

In those patients in which a degree of depression accompanies the anxiety, suicidal tendencies may be present and protective measures may be required. The least amount of drug that is feasible should be available to the patient.

Patients taking TRANXENE tablets for prolonged periods should have blood counts and liver function tests periodically. The usual precautions in treating patients with impaired renal or hepatic function should also be observed.

In elderly or debilitated patients, the initial dose should be small, and increments should be made gradually, in accordance with the response of the patient, to preclude ataxia or excessive sedation.

Information for Patients:

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

ADVERSE REACTIONS

The side effect most frequently reported was drowsiness. Less commonly reported (in descending order of occurrence) were: dizziness, various gastrointestinal complaints, nervousness, blurred vision, dry mouth, headache, and mental confusion. Other side effects included insomnia, transient skin rashes, fatigue, ataxia, genitourinary complaints, irritability, diplopia depression, tremor and slurred speech.

There have been reports of abnormal liver and kidney function tests and of decrease in hematocrit.

Decrease in systolic blood pressure has been

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Because of the lack of sufficient clinical experience, TRANXENE tablets are not recommended for use in patients less than 9 years of age.

Physical and Psychological Dependence:

Withdrawal symptoms (similar in character to those noted with barbiturates and alcohol) have occurred following abrupt discontinuance of clorazepate. Withdrawal symptoms associated with the abrupt discontinuation of benzodiazepines have included convulsions, delirium, tremor, abdominal and muscle cramps, vomiting, sweating, nervousness, insomnia, irritability, diarrhea, and memory impairment. The more severe withdrawal symptoms have usually been limited to those patients who had received excessive doses over an extended period of time. Generally milder withdrawal symptoms have been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months. Consequently, after extended therapy, abrupt discontinuation of clorazepate should generally be avoided and a gradual dosage tapering schedule followed.

Caution should be observed in patients who are considered to have a psychological potential for drug dependence.

Evidence of drug dependence has been observed in dogs and rabbits which was characterized by convulsive seizures when the drug was abruptly withdrawn or the dose was reduced; the syndrome in dogs could be abolished by administration of clorazepate.

Usage in Pregnancy:

An increased risk of congenital malformations associated with the use of minor tranquilizers (chlordiazepoxide, diazepam, and meprobamate) during the first trimester of pregnancy has been suggested in several studies. Clorazepate dipotassium, a benzodiazepine derivative, has not been studied adequately to determine whether it, too, may be associated with an increased risk of fetal abnormality. Because use of these drugs is rarely a matter of urgency, their use during this period should almost always be avoided. The possibility that a woman of childbearing potential may be pregnant at the time of institution of therapy should be considered. Patients should be advised that if they become pregnant during therapy or intend to become pregnant they should communicate with their physician about the desirability of discontinuing the drug.

Usage during Lactation:

TRANXENE tablets should not be given to nursing mothers since it has been reported that nordiazepam is excreted in human breast milk.

PRECAUTIONS

In those patients in which a degree of depression accompanies the anxiety, suicidal tendencies may be present and protective measures may be required. The least amount of drug that is feasible should be available to the patient.

Patients taking TRANXENE tablets for prolonged periods should have blood counts and liver function tests periodically. The usual precautions in treating patients with impaired renal or hepatic function should also be observed.

In elderly or debilitated patients, the initial dose should be small, and increments should be made gradually, in accordance with the response of the patient, to preclude ataxia or excessive sedation.

Information for Patients:

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

ADVERSE REACTIONS

The side effect most frequently reported was drowsiness. Less commonly reported (in descending order of occurrence) were: dizziness, various gastrointestinal complaints, nervousness, blurred vision, dry mouth, headache, and mental confusion. Other side effects included insomnia, transient skin rashes, fatigue, ataxia, genitourinary complaints, irritability, diplopia depression, tremor and slurred speech.

There have been reports of abnormal liver and kidney function tests and of decrease in hematocrit.

Decrease in systolic blood pressure has been observed.

DOSAGE AND ADMINISTRATION

For the symptomatic relief of anxiety:

TRANXENE (clorazepate dipotassium) T-TAB® tablets are administered orally in divided doses. The usual daily dose is 30 mg. The dose should be adjusted gradually within the range of 15 to 60 mg daily in accordance with the response of the patient. In elderly or debilitated patients it is advisable to initiate treatment at a daily dose of 7.5 to 15 mg.

TRANXENE tablets may also be administered in a single dose daily at bedtime; the recommended initial dose is 15 mg. After the initial dose, the response of the patient may require adjustment of subsequent dosage. Lower doses may be indicated

(OVER)

cholestasis with minimal hepatocellular damage was found, but lobular architecture remained well preserved.

Eighteen rhesus monkeys were given oral doses of clorazepate dipotassium from 3 to 36 mg/kg daily for 52 weeks. All treated animals remained similar to control animals. Although total leucocyte count remained within normal limits it tended to fall in the female animals on the highest doses.

Examination of all organs revealed no alterations attributable to clorazepate dipotassium. There was no damage to liver function or structure.

Reproduction Studies:

Standard fertility, reproduction, and teratology studies were conducted in rats and rabbits. Oral doses in rats up to 150 mg/kg and in rabbits up to 15 mg/kg produced no abnormalities in the fetuses. TRANXENE (clorazepate dipotassium) did not alter the fertility indices or reproductive capacity of adult animals. As expected, the sedative effect of high doses interfered with care of the young by their mothers (see *Usage in Pregnancy*).

HOW SUPPLIED

TRANXENE® (clorazepate dipotassium) is supplied as:

3.75 mg blue-colored, scored T-TAB® tablets:
Bottles of 100.....(NDC 0074-4389-13).
Bottles of 500.....(NDC 0074-4389-53).
ABBO-PAC® unit dose packages:
100.....(NDC 0074-4389-11).

7.5 mg peach-colored, scored T-TAB® tablets:
Bottles of 100.....(NDC 0074-4390-13).
Bottles of 500.....(NDC 0074-4390-53).
ABBO-PAC® unit dose packages:
100.....(NDC 0074-4390-11).

15 mg lavender-colored, scored T-TAB® tablets:
Bottles of 100.....(NDC 0074-4391-13).
Bottles of 500.....(NDC 0074-4391-53).
ABBO-PAC® unit dose packages:
100.....(NDC 0074-4391-11).

TRANXENE®-SD™ 22.5 mg tan-colored, single dose tablets:
Bottles of 100.....(NDC 0074-2997-13).

TRANXENE®-SD™ HALF STRENGTH 11.25 mg blue-colored, single dose tablets:
Bottles of 100.....(NDC 0074-2699-13).

T-TAB, tablet appearance and shape are trademarks of Abbott Laboratories.

Recommended storage: Store below 77°F (25°C)

U.S. Design Pat. No. D-300,879

FEB - 7 2002

APPROVED

ABBOTT LABORATORIES
NORTH CHICAGO, IL60064, U.S.A.

PRINTED IN U.S.A.

034490

03-4490-R13-Rev. March, 1994

TRANXENE® CLORAZEPATE DIPOTASSIUM

T-TAB® Tablets (Nos. 4389, 4390, 4391)

TRANXENE®-SD™ &
TRANXENE®-SD™ HALF STRENGTH
Tablets (Nos. 2997, 2699)

2-8

Labeling: S.A.R. 062 (M)
NDA No: 17-105 Rec'd 6 Sep
Reviewed By: _____

associated with somatic disease states, careful attention must be paid to possible drug interaction with concomitant medication.

In bioavailability studies with normal subjects, the concurrent administration of antacids at therapeutic levels did not significantly influence the bioavailability of TRANXENE tablets.

OVERDOSAGE

Overdosage is usually manifested by varying degrees of CNS depression ranging from slight sedation to coma. As in the management of overdosage with any drug, it should be borne in mind that multiple agents may have been taken.

The treatment of overdosage should consist of the general measures employed in the management of overdosage of any CNS depressant. Gastric evacuation either by the induction of emesis, lavage, or both, should be performed immediately. General supportive care, including frequent monitoring of the vital signs and close observation of the patient, is indicated. Hypotension, though rarely reported, may occur with large overdoses. In such cases the use of agents such as Levophed® Bitartrate (norepinephrine bitartrate injection, USP) or Aramine® Injection (metaraminol bitartrate injection, USP) should be considered.

While reports indicate that individuals have survived overdoses of clorazepate dipotassium as high as 450 to 675 mg, these doses are not necessarily an accurate indication of the amount of drug absorbed since the time interval between ingestion and the institution of treatment was not always known. Sedation in varying degrees was the most common physiological manifestation of clorazepate dipotassium overdosage. Deep coma when it occurred was usually associated with the ingestion of other drugs in addition to clorazepate dipotassium.

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.

ANIMAL PHARMACOLOGY AND TOXICOLOGY

Studies in rats and monkeys have shown a substantial difference between doses producing tranquilizing, sedative and toxic effects. In rats, conditioned avoidance response was inhibited at an oral dose of 10 mg/kg; sedation was induced at 32 mg/kg; the LD_{50} was 1320 mg/kg. In monkeys aggressive behavior was reduced at an oral dose of 0.25 mg/kg; sedation (ataxia) was induced at 7.5 mg/kg; the LD_{50} could not be determined because of the emetic effect of large doses, but the LD_{50} exceeds 1600 mg/kg.

Twenty-four dogs were given clorazepate dipotassium orally in a 22-month toxicity study; doses up to 75 mg/kg were given. Drug-related changes occurred in the liver; weight was increased and cholestasis with minimal hepatocellular damage was found, but lobular architecture remained well preserved.

Eighteen rhesus monkeys were given oral doses of clorazepate dipotassium from 3 to 36 mg/kg daily for 52 weeks. All treated animals remained similar to control animals. Although total leucocyte count remained within normal limits it tended to fall in the female animals on the highest doses.

Examination of all organs revealed no alterations attributable to clorazepate dipotassium. There was no damage to liver function or structure.

Reproduction Studies:

Standard fertility, reproduction, and teratology studies were conducted in rats and rabbits. Oral doses in rats up to 150 mg/kg and in rabbits up to 15 mg/kg produced no abnormalities in the fetuses. TRANXENE (clorazepate dipotassium) did not alter the fertility indices or reproductive capacity of adult animals. As expected, the sedative effect of high doses interfered with care of the young by their mothers (see *Usage in Pregnancy*).

HOW SUPPLIED

TRANXENE® (clorazepate dipotassium) is supplied as:

3.75 mg blue-colored, scored T-TAB® tablets:
Bottles of 100.....(NDC 0074-4389-13).
Bottles of 500.....(NDC 0074-4389-53).
ABBO-PAC® unit dose packages:
100.....(NDC 0074-4389-11).

7.5 mg peach-colored, scored T-TAB® tablets:
Bottles of 100.....(NDC 0074-4390-13).
Bottles of 500.....(NDC 0074-4390-53).
ABBO-PAC® unit dose packages:
100.....(NDC 0074-4390-11).

15 mg lavender-colored, scored T-TAB® tablets:
Bottles of 100.....(NDC 0074-4391-13).
Bottles of 500.....(NDC 0074-4391-53).
ABBO-PAC® unit dose packages:
100.....(NDC 0074-4391-11).

in the elderly patient. Drowsiness may occur at the initiation of treatment and with dosage increment.

TRANXENE-SD (22.5 mg) tablets may be administered as a single dose every 24 hours. This tablet is intended as an alternate dosage form for the convenience of patients stabilized on a dose of 7.5 mg tablets three times a day. TRANXENE-SD tablets should not be used to initiate therapy.

TRANXENE-SD HALF STRENGTH (11.25 mg) tablets may be administered as a single dose every 24 hours. This tablet is intended as an alternate dosage form for the convenience of patients stabilized on a dose of 3.75 mg tablets three times a day. TRANXENE-SD HALF STRENGTH should not be used to initiate therapy.

For the symptomatic relief of acute alcohol withdrawal:

The following dosage schedule is recommended:

1st 24 hours (Day 1)	30 mg initially; followed by 30 to 60 mg in divided doses
2nd 24 hours (Day 2)	45 to 90 mg in divided doses
3rd 24 hours (Day 3)	22.5 to 45 mg in divided doses
Day 4	15 to 30 mg in divided doses

Thereafter, gradually reduce the daily dose to 7.5 to 15 mg. Discontinue drug therapy as soon as patient's condition is stable.

The maximum recommended total daily dose is 90 mg. Avoid excessive reductions in the total amount of drug administered on successive days.

As an Adjunct to Antiepileptic Drugs:

In order to minimize drowsiness, the recommended initial dosages and dosage increments should not be exceeded.

Adults: The maximum recommended initial dose in patients over 12 years old is 7.5 mg three times a day. Dosage should be increased by no more than 7.5 mg every week and should not exceed 90 mg/day.

Children (9-12 years): The maximum recommended initial dose is 7.5 mg two times a day. Dosage should be increased by no more than 7.5 mg every week and should not exceed 60 mg/day.

DRUG INTERACTIONS

If TRANXENE (clorazepate dipotassium) is to be combined with other drugs acting on the central nervous system, careful consideration should be given to the pharmacology of the agents to be employed. Animal experience indicates that clorazepate dipotassium prolongs the sleeping time after hexobarbital or after ethyl alcohol, increases the inhibitory effects of chlorpromazine, but does not exhibit monoamine oxidase inhibition. Clinical studies have shown increased sedation with concurrent hypnotic medications. The actions of the benzodiazepines may be potentiated by barbiturates, narcotics, phenothiazines, monoamine oxidase inhibitors or other antidepressants.

If TRANXENE tablets are used to treat anxiety associated with somatic disease states, careful attention must be paid to possible drug interaction with concomitant medication.

In bioavailability studies with normal subjects, the concurrent administration of antacids at therapeutic levels did not significantly influence the bioavailability of TRANXENE tablets.

OVERDOSAGE

Overdosage is usually manifested by varying degrees of CNS depression ranging from slight sedation to coma. As in the management of overdosage with any drug, it should be borne in mind that multiple agents may have been taken.

The treatment of overdosage should consist of the general measures employed in the management of overdosage of any CNS depressant. Gastric evacuation either by the induction of emesis, lavage, or both, should be performed immediately. General supportive care, including frequent monitoring of the vital signs and close observation of the patient, is indicated. Hypotension, though rarely reported, may occur with large overdoses. In such cases the use of agents such as Levophed® Bitartrate (norepinephrine bitartrate injection, USP) or Aramine® Injection (metaraminol bitartrate injection, USP) should be considered.

While reports indicate that individuals have survived overdoses of clorazepate dipotassium as high as 450 to 675 mg, these doses are not necessarily an accurate indication of the amount of drug absorbed since the time interval between ingestion and the institution of treatment was not always known. Sedation in varying degrees was the most common physiological manifestation of clorazepate dipotassium overdosage. Deep coma when it occurred was usually associated with the ingestion of other drugs in addition to clorazepate dipotassium.

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 17-105/S-059/S-062

ADMINISTRATIVE DOCUMENTS

REGULATORY PROJECT MANAGER
LABELING REVIEW

Date:	January 25, 2002
Drug/NDA/Sponsor:	Tranxene (clorazepate dipotassium) Capsules and Tablets; NDA 17-105; Abbott Laboratories
Drug/NDA/Sponsor:	Tranxene Capsules; NDA 17-107; Sanofi
Indication:	Generalized Anxiety Disorder (GAD)
Supplements:	

NDA	Supplement	Dated	Action
Tranxene Capsules (NDA 17-107) Sanofi			
17-107	SLR-001	6-21-79	AP Letter dated 12-12-79
Tranxene (clorazepate dipotassium) Capsules and Tablets (NDA 17-105) Abbott			
17-105	SES-039	12-12-80	AP Letter Dated 1-29-81
17-105	SLR-059	4-16-87	Open Supplement
17-105	SLR-062	9-10-87, and amended on 12-23-87, and 6-7-94	IR Letters Dated 3-26-93 and 5-6-93; Open Supplement

Notes of interest:

1. The original NDA for Tranxene was approved with the immediate release formulation tablets. The sponsor subsequently submitted chemistry supplements which provided for the Tranxene-SD (sustained release/once daily) and the Tranxene-SD Half Strength (sustained release/once daily) formulations. Current Agency policy would now require separate NDAs.

2. Although Sanofi-Synthelabo has an approved NDA, 17-107, for Tranxene capsules, this drug has never been marketed. The file is unclear as to the circumstances behind 2 companies having the same approved product but I assume that it entailed some business partnership.

REVIEW

17-105/SLR-059
Date: 4-16-87
Label Code: 03-4288-R7
CBE: Yes
Reviewed by Medical Officer/DDMAC: Yes, acceptable

This supplement provides for the placement of a revision date, a substance symbol, and the use of the "T-Tab" symbol in labeling.

Notes of Interest:

- This supplement was submitted secondary to DDMAC concerns related to the labeling and possible medication errors related to the "T-Tab" name in describing Tranxene T-Tab tablets. The sponsor adequately responded to the Agency's concerns, and this is noted by the medical

17-105/SLR-062
Date: 9-10-87, and amended on 12-23-87 and 6-7-94
Label Code: 03-4490-R13
CBE: Yes
Reviewed by Medical Officer: Yes, acceptable

This supplement provides for revisions in labeling to incorporate additional information on withdrawal problems associated with benzodiazepines, additional pharmacokinetic information, and editorial revisions. This supplement responded to an Agency letter dated 7-8-87 requesting revisions to product labeling.

Notes of Interest:

- The Agency disagreed with the initial changes submitted by Abbott in their correspondence dated 9-10-87. This was conveyed in a telephone conversation by the PM to Abbott dated 9-15-87 (also see clinical review/TL note dated 9-10-87, and 9-25-87, respectively). Abbott subsequently submitted an amendment to this application dated 12-23-87 which incorporated the Agency's revised language. These changes were found to be acceptable by the PM, and an approvable letter issued dated 2-17-88 only requesting FPL.
- The sponsor never submitted FPL as requested in the Agency letter dated 2-17-88. A second letter issued dated 3-26-93 requesting that the sponsor submit FPL. This letter was returned to the Agency for some unknown reason. Another Agency letter dated 5-6-93 issued which

requested that the sponsor submit FPL. The sponsor responded to this letter in a submission dated 6-7-94.

- I was unable to retrieve the 6-7-94 submission that contained the FPL for SLR-062. However, the periodic report dated 7-19-94 contained a sample of this labeling, and I used it for comparison purposes against the last approved labeling for Tranxene (17-105/SES-039). Additionally, I found a telecon in the file dated 6-28-94 between the PM and Abbott stating that the labeling submitted on 6-7-94 was adequate and "reveal all changes are adequately

- The sponsor submitted labeling which incorporates the Agency's requested changes, verbatim. However, they also moved the **Clinical Pharmacology** subsection from **ANIMAL AND CLINICAL PHARMACOLOGY** (at the end of the labeling) an created a new section entitled **CLINICAL PHARMACOLOGY** after the **DESCRIPTION** section. The FPL also renames the [redacted]tion to **ANIMAL PHARMACOLOGY AND TOXICOLOGY**. All of the previous information carried over to the new **CLINICAL PHARMACOLOGY** section, and the sponsor has added some new information to this section.

CONCLUSIONS

1. The above labeling supplements only provide for those revisions as stated above for these open supplements.

2. [redacted]

4. The medical officer and DDMAC concur with the CBE labeling revisions submitted to NDA 17-105/SLR-059/SLR-062. If the medical officer concurs with the additional changes to SLR-062, under the **CLINICAL PHARMACOLOGY** section, I recommend that an approval letter issue to these supplemental applications.

Paul David, R.Ph., Regulatory Project Manager

Robbin Nighswander, R.Ph., Supervisory Regulatory Health Officer

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Paul David
2/4/02 08:20:37 AM
CSO

Robbin Nighswander
2/4/02 02:36:31 PM
CSO

RECORD OF TELEPHONE CONVERSATION

DATE: June 28, 1994

FROM: Gary Magistrelli, Ph.D.(Abbott)
(Phone: 708-937-0859)

TO: Merril J. Mille
Division of Neuropharmacological Drug Products,
HFD-120

SUBJECT: NDA 17-105 (TRANXENE)

INITIATED BY: HFD-120

Per Dr. Laughren, the firm was notified that S-062 may be implemented under "Changes Being Effected." A reassessment of the provisions of the supplement reveal all changes are adequately supported.

6/28/94
Caryn Stumler for Merril J. Mille, CSO

cc:
ORIG NDA 17-105
HFD-120
HFD-120/Mille

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

MAY - 6 1993

NDA 17-105/S-062

Abbott Laboratories
Pharmaceuticals Products Division
Dept. 491, Bldg. AP6B/1
One Abbott Park Road
Attention: Mr. Roland Catherall
Abbott Park, Illinois 60064-3500

Dear Mr. Catherall:

Reference is made to your New Drug Application submitted pursuant to section 505(b) of the Federal Food, Drug and Cosmetic Act for Tranxene (Clorazepate monopotassium) Capsules and to your supplement S-062 submitted on September 10, 1987.

We also refer to an Agency letters dated February 17, 1988, and March 26, 1993. The latter letter provides text identical to that provided below, however, it was returned undelivered by the U.S. Postal Service for an unknown reason.

We note that supplemental application S-062 provides revised draft labeling regarding dependence and withdrawal symptoms associated with benzodiazepines. Our letter of February 17, 1988, permitted these changes and requested submission of final printed labeling (FPL) and implementation of the new labeling within 120 days or at the next printing, whichever is sooner.

During an administrative review, it has come to our attention that FPL incorporating the changes provided by supplement S-062 was neither submitted to this NDA nor put into effect despite the 120 day timetable.

Therefore, we request the submission of a written response to this letter describing your commitment to the submission of FPL incorporating the requested changes and a proposed implementation date, or a reasonable explanation as to why these changes have not been implemented.

If an adequate response is not received within 60 days from the date of this letter, we will inform the Office of Compliance that we believe your current labeling does not provide an adequate description for the safe and effective use of Tranxene.

Should any questions arise concerning this NDA, please contact Mr. Merril Mille, Regulatory Management Officer, at (301) 443-3830.

Sincerely yours,

5/6/92

Paul Leber, M.D.
Director
Division of Neuropharmacological
Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc: ORIG NDA 17-105
HFD-120
HFD-120/PLeber
HFD-120/JKnudsen/TLaughren
HFD-120/MMille:5/5/93
DT:05/5/93/MJM
FT:

JN 5-5-93

Doc # F:\Mille\N17105.340

CORRESPONDENCE

561

NDA 17-105/S-062

MAR 26 1993

Abbott Laboratories
Pharmaceuticals Products Division
One Abbott Park Road
Attention: Christopher Smith
Abbott Park, Illinois 60064-3500

Dear Mr. Smith:

Reference is made to your New Drug Application submitted pursuant to section 505(b) of the Federal Food, Drug and Cosmetic Act for Tranxene (Clorazepate monopotassium) Capsules and to your supplement S-062 submitted on September 10, 1987.

We also refer to an Agency letter dated February 17, 1988.

We note that supplemental application S-062 provided revised draft labeling regarding dependence and withdrawal symptoms associated with benzodiazepines. Our letter of February 17, 1988, permitted these changes and requested submission of final printed labeling (FPL) and implementation of the new labeling within 120 days or at the next printing, whichever is sooner.

During an administrative review, it has come to our attention that FPL incorporating the changes provided by supplement S-062 was neither submitted to this NDA nor put into effect despite the 120 day timetable.

Therefore, we request the submission of a written response to this letter describing your commitment to the submission of FPL incorporating the requested changes and a proposed implementation date, or a reasonable explanation as to why these changes have not been implemented.

If an adequate response is not received within 60 days from the date of this letter, we will inform the Office of Compliance that we believe your current labeling does not provide an adequate description for the safe and effective use of Tranxene.

Should any questions arise concerning this NDA, please contact Mr. Merril Mille, Regulatory Management Officer, at (301) 443-3830.

Sincerely yours,

3/26/93

Paul Leber, M.D.
Director
Division of Neuropharmacological
Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc: ORIG NDA 17-105
HFD-120
HFD-120/PLeber
HFD-120/JKnudsen/TLaughren 3-25-93
HFD-120/MMille:3/18/93
DT:03/18/93/MJM
FT:3/25/93/gt
spell checked:3/25/93/gt

Doc # F:\Mille\N17105.319

CORRESPONDENCE

HFD-130

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 25, 1993

FROM: Merril J. Mille, R. Ph.
Senior Regulatory Management Officer, HFD-120

SUBJECT: TRANXENE/ Supplement S-062

TO: File, N 17-105

During an administrative review, it was noted that the *Physical and Psychological Dependence* subsection of WARNINGS in Tranxene labeling was not consistent with other benzodiazepine products. On closer scrutiny, it was discovered that the "class" language for this subsection was permitted with draft labeling under S-062 in an Agency letter dated February 17, 1988. However, it appears that the FPL was never submitted and the changes were never implemented.

In order to bring the Tranxene labeling into compliance, a letter should issue requesting a plan for implementation of the changes provided under S-062. If the firm does not respond adequately or in a timely fashion, we should consider notifying the Office of Compliance.

Particulars:
S-062 is found under Vol. 49.1 See Labeling review by Ms. L. Macturk describing the labeling negotiations for this supplement.

Annual report (Y-024), found in vol. 56.1, indicates the provisions of S-062 are not incorporated into current labeling.

cc:
ORIG NDA 17-105
HFD-120
HFD-120/MMille

Doc#: E:\wpfiles\memo\Tranxene

NDA 17-105/S-062

Abbott Laboratories
Attention: Christopher Smith
Abbott Park, Illinois 60064

FEB 17 [redacted]

Dear Mr. Smith:

Please refer to your supplemental new drug application dated September 10, 1987, submitted pursuant to section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Tranxene (clorazepate dipotassium) Tablets and Capsules. We also refer to your amendment dated December 23, 1987.

The supplemental application provides revised labeling for Tranxene Tablets to warn of the withdrawal reactions of benzodiazepine products.

We have completed our review of this supplemental application. The changes proposed in the supplement as amended December 23, 1987, are permissable. Please submit final printed labeling incorporating the changes contained in the annotated labeling submitted December 23, 1987. This labeling should be placed in use within 120 days or at the next printing of the labeling whichever is sooner.

If you have any questions concerning this NDA, please contact Mr. Richard Potter, Consumer Safety Officer, at (301) 443-3830.

Sincerely yours,

Paul Leber, M.D.
Director
Division of Neuropharmacological
Drug Products
Office of Drug Research and Review
Center for Drug Evaluation and Research

cc: ORIG NDA
HFN-120
HFN-120/Potter R.P. 2-16-88
Laughren
Leber
HFN-231/Chang
rd/rp/2/1/88
ft/eb/2/16/88
Doc # 2539c
SUPPLEMENT PERMISSABLE

CSO Review of Labeling

NDA Number: 17-105/S-062

FEB 17 1988

Drug: Tranxene (clorazepate dipotassium) Capsules and Tablets

Sponsor: Abbott Laboratories

Date of Submission: December 23, 1987

Abbott submitted a response on September 10, 1987 to the Agency's letter requesting labeling revisions regarding dependence and withdrawal symptoms associated with benzodiazepines. We informed the company by telephone call (Potter, 9-15-87) that we did not agree with their response. The company has now submitted a new response based on that telephone call. The new response contains the change that we requested in our telephone call of 9-15-87.

The company has deleted the sentence that we objected to: [redacted]

The December 23 response remains the same as the September 10, 1987 response in every other respect.

Consequently, the company has complied with our requests reagarding labeling for benzodiazepine withdrawal. The supplement, as amended, can be permissable. Final printed labeling incorporating the changes should be requested before the supplement can be permitted.

Richard Potter 2-1-88
Richard Potter/date

John S Lumis 2/4/88
Supervisory CSO Signature/date

cc:
Orig. NDA
HFN-120
HFN-120/Potter / T Laughren
HFN-231/Chang
Doc # 2538c

SEP 28 1987

Review of Proposed Labeling

NDA 17-105/S-062

Drug: Tranxene (clorazepate dipotassium) Capsules

Sponsor: Abbott

Date of Submission: September 10, 1987

In response to an agency letter dated July 8, 1987 requesting labeling revisions regarding dependence and withdrawal symptoms associated with benzodiazepines, Abbott has submitted this supplement.

In our July 8, 1987 letter, we requested two changes. Abbott's response to each follows.

1. We requested that the firm replace the first paragraph of Warnings, "Physical and Psychological Dependence" with:

> "Withdrawal symptoms (similar in character to those noted with barbiturates and alcohol) have occurred following abrupt discontinuance of clorazepate. Withdrawal symptoms associated with the abrupt discontinuation of [redacted] benzodiazepines have included convulsions, delirium, tremor, abdominal and muscle cramps, vomiting, sweating, nervousness, insomnia, irritability, diarrhea, and memory impairment. The more severe withdrawal symptoms have usually been limited to those patients who had received excessive doses over an extended period of time. Generally milder withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines taken continuously at therapeutic levels for several months. Consequently, after extended therapy, abrupt discontinuation of clorazepate should generally be avoided and a gradual dosage tapering schedule followed."

ABBOTT RESPONDED by adding most of the paragraph. However, they made two changes:

a. As the second sentence of the section, they added: [redacted]

b. They removed [redacted]" from the sentence which was to have read: "Withdrawal symptoms associated with the abrupt discontinuation of [redacted] benzodiazepines have included convulsions, delirium, tremor, ... ".

2. We requested that the firm add an "Information for Patients" section and include the following paragraph:

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

ABBOTT RESPONDED by adding the paragraph but changing ——— " to "essential".

In addition, the firm has initiated other changes in the labeling:

1. "Tablets" and "clorazepate dipotassium" have been added throughout the label.

2. In ——— Clinical Pharmacology, "Absorption-Excretion", they have expanded the section to two paragraphs based on new pharmacokinetic data derived from Abbott studies:

> "Since orally administered clorazepate dipotassium is rapidly decarboxylated to form nordiazepam, there is essentially no circulating parent drug. Nordiazepam, the primary metabolite, quickly appears in the blood stream and is eliminated from the plasma with an apparent half-life of about ——— Plasma levels of nordiazepam increase proportionally with the TRANXENE dose and show moderate accumulation with repeated administration. The protein binding of nordiazepam in plasma is high (97-98%).
>
> Within 10 days after oral administration of a 15 mg (50 uCi) dose of ^{14}C-TRANXENE to two volunteers, 62-67% of the radioactivity was excreted in the urine and 15-19% was eliminated in the feces. Both subjects were still excreting measurable amounts of radioactivity in the urine (about 1% of the ^{14}C-dose) on day ten. Nordiazepam is further metabolized by hydroxylation. The major urinary metabolite is conjugated oxazepam (3-hydroxynordiazepam), and smaller amounts of conjugated p-hydroxynordiazepam and nordiazepam are also found in the urine."

Laurie Macturk 9-23-87

Laurie Macturk
Clinical Review Assistant

Group Leader's Conclusions and Recommendations for Action Letter

9-25-87

I agree with the sponsor's deletion of the term ~~_____~~ from the 2nd sentence of the 1st paragraph of our proposed warning statement

Thomas P. Laughren MD
GL, PDPG

cc:
NDA 17-105
HFN-120
HFN-120/Macturk
Laughren
Potter
rd/mlm/9/23/87
Doc 2106k

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date MAY 13 1987

NDA No. 17-105

Abbott Laboratories
Abbott Park
North Chicago, Illinois 60064

Attention: W. M. Nelson

Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Tranxene Capsules

NDA Number: 17-105

Supplement Number: S-059

Date of Supplement: April 16, 1987

Date of Receipt: April 22, 1987

All communications concerning this NDA should be addressed as follows:

Center for Drugs and Biologics, HFN-120
Attention: Document Control, Room 10B-30
5600 Fishers Lane
Rockville MD 20857

Sincerely Yours
Marsha T. Cay
For John S. Purvis
Division of Neuropharmacological Drug Products
Center for Drugs and Biologics

cc:
NDA File
HFN-120 File
CSO File

FORM FDA 3217b (2/86)

ABBOTT

NBA NO. 17-105 REF. NO. S-059

NDA SUPPL FOR Labeling Supp

Pharmaceutical Products Division

Abbott Laboratories
Abbott Park, Illinois 60064

Noted
File
TWC 4/24/87

April 16, 1987 TWCavanaugh:t.
HFN-240 (Tranxene, Abbott; T-TAB, Abbott)
HFN-244 (TWC), ~~HFA-224~~
ORIG. (HFN-120, NDA 17-105, NDA 17-107)
HFN-33 (Drug Product Report #73059; #73094, #73141)

Mr. Thomas Cavanaugh
Division of Drug Advertising and Labeling
HFN-244, Room 10B-04
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Reviewed by Drug Advertising and Labeling: satisfactorily addresses their concerns
NAL. Kleon 10/27/87

Re: **Tranxene® T-Tab™ Tablets (clorazepate dipotassium)**
NDA 17-105

Dear Mr. Cavanaugh:

Concerning our telephone calls on March 27 and 31 and your letter dated April 2, 1987 about a Tranxene promotional piece identified as 703-503, you asked Abbott Laboratories to respond in writing to the various concerns you raised. Two of your concerns relate to the package insert included with the subject promotional piece. You pointed out that the revision date and scheduled substance symbol were missing on the package insert. Enclosed is our most recent package insert which corrects these deficiencies.

You also inquired about the use of "T-Tab" to describe Tranxene T-Tab Tablets and our suggestion that physicians can prescribe the drug by the use of this term. There is apparently a concern by some pharmacists that confusion could occur when the drug is prescribed. As we discussed, we do not believe confusion will occur when Tranxene is prescribed even when only the term "T-Tab" is used. This is because the product name is not the same as other drugs (T-Tab versus K-Tab) and the dosage requirements will distinguish the drugs even when a prescription is so poorly written that a pharmacist cannot read the tradename. You should also be aware that pharmacists have been informed of the name change for Tranxene by a letter (copy attached) sent to all retail pharmacies shortly after the name change was implemented.

To insure that our promotional materials do not confuse our customers, we intend to use, and have used, the term "T-Tab" to describe a particular dosage form of Tranxene. Consequently, a discussion of "T-Tab" in sales aids and similar promotional materials will, always occur in the context that it is a dosage form of Tranxene.

Delivery of Tranxene promotional materials to the Agency were inadvertently delayed because of an administrative problem. All Tranxene promotional materials have been sent to the Agency as of this date and we will make every effort to deliver them in a timely manner in the future.

For your information, the April supplement of the PDR has been changed to reflect the new product name. Because of publication dates, this was our first opportunity to revise the PDR.

I trust this letter adequately addresses your concerns.

Sincerely,

W. M. Nelson
Regulatory Affairs, D491 AP10
(312) 937-6845

WMN/314/gs

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date SEP 22 1987

NDA No. 17-105

Abbott Laboratories
Pharmaceutical Products Division
Abbott Park, Illinois 60064

Attention: Donald F. Hudson, Ph.D.

Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Tranxene

NDA Number: 17-105

Supplement Number: S-062

Date of Supplement: September 10, 1987

Date of Receipt: September 10, 1987

All communications concerning this NDA should be addressed as follows:

Center for Drugs and Biologics, HFN-120
Attention: Document Control, Room 10B-30
5600 Fishers Lane
Rockville MD 20857

Sincerely yours
Marcia T. Cruz
For John S. Davis
Division of Neuropharmacological Drug Products
Center for Drugs and Biologics

cc:
NDA File
HFN-120 File
CSO File

FORM FDA 3217b (2/86)

ABBOTT

NDA NO. 17-105 REF. NO. S-062

NDA SUPPL FOR Labeling Rev

DF Henderson

ORIGINAL

Pharmaceutical Products Division

Abbott Laboratories
Abbott Park, Illinois 60064

September 10, 1987

Division of Neuropharmacological Drug Products, HFN-120
Document Control Room 10B-34
Center for Drugs and Biologics
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

SPECIAL SUPPLEMENT - CHANGES BEING EFFECTED

RECEIVED
NATIONAL CENTER
SEP 10 1987
HFN-120
FOR DRUGS & BIOLOGICS

RE: Tranxene® (clorazepate dipotassium)
NDA 17-105
Supplement

Dear Sir or Madam:

In response to your letter dated July 8, 1987, we are enclosing an annotated copy of proposed Tranxene labeling incorporating additional information on withdrawal problems associated with benzodiazepines, additional information on pharmacokinetics derived from Abbott studies, and editorial changes. We are submitting the following revisions of the proposed Physical and Psychological Dependence subsection for your consideration.

We have removed " ——— "rom the proposed sentence, "Withdrawal symptoms associated with the abrupt discontinuation of ——— benzodi- ——— have included ..." Including the phrase ——— in this sentence implies that these symptoms occur only after termination of long-acting benzodiazepines. Since that is not the case, suggesting that the list of withdrawal symptoms is specifically associated with long-acting benzodiazepines would be misleading.

In contrast, evidence in the literature indicates that withdrawal symptoms associated with long-acting and short-acting benzodiazepines differ in severity and frequency. Bixler[1] investigated the occurrence of rebound insomnia following benzodiazepine withdrawal in a placebo-controlled study. Bixler observed that patients withdrawn from short-acting benzodiazepines experienced significantly higher rates of rebound insomnia than did the placebo group. He also studied the extended withdrawal period for the long-acting benzodiazepines and noted that the rate of rebound insomnia was similar for placebo and active drug groups on nights four through fifteen of withdrawal.

Busto et al[2] reported from a double-blind placebo-controlled study that withdrawal symptoms occurred within the first day following abrupt discontinuation of short-acting benzodiazepines whereas withdrawal symptoms did not appear until the third to eighth day following abrupt discontinuation of long-acting compounds. In this study, patients who were withdrawn from short-acting compounds rated their withdrawal symptoms as being more severe than did the patients withdrawn from long-acting compounds.

Tyrer et al[3] conducted a placebo crossover study investigating the incidence of withdrawal symptoms associated with a long- and short-acting benzodiazepine. The authors observed that the majority of patients withdrawn from a short-acting benzodiazepine experienced withdrawal symptoms associated with a rapid decrease in plasma drug levels. Patients who had withdrawal symptoms after discontinuation of a long-acting benzodiazepine also demonstrated a rapid decrease in plasma drug levels (desmethyldiazepam). The authors conclude from this evidence that, "...withdrawal phenomenon are related to the rate at which circulating benzodiazepines and their active metabolites are excreted and metabolized."

Hollister[4] related a drug's half-life to the possible severity of withdrawal. He stated that "withdrawal reactions are of the greatest severity and intensity with drugs that have a rapid rate of disappearance." He further noted that drugs with a plasma T 1/2 (plasma half-life) of 8-20 hours produce the most severe reactions because of rapid decline in levels. Drugs with plasma T 1/2 of more than 36 hours (including active metabolites) have a built-in tapering action, and withdrawal reactions are milder and attenuated.

Based on this and other evidence, we propose the addition of the following sentence to the labeling:

_____

_____

_____

We feel that the above mentioned recommendations clarify the proposed labeling presented in the July 8 letter and are consistent with the intent of that proposal. To have revised package enclosures in use by November 1987 requires that we order their printing no later than September 18, 1987. We plan to do so unless we receive an objection from you prior to that date. Final printed labeling will be submitted when available.

Sincerely,

DF Hudson

Donald F. Hudson, Ph.D.
Director, PPD Regulatory Affairs
(312) 937-7494

REFERENCES:

1. Bixler, E.O., Kales, J.D., Kales, A., Rebound Insomnia and Elimination Half-life: Assessment of Individual Subject Response, J Clin Pharmacol 25:115-124, 1985.

2. Busto, V., Sellers, E.M., Narazo, C.A., et al, Withdrawal Reaction after Long-Term Therapeutic Use of Benzodiazepines, N Engl J Med 315(14):854-859, October 2, 1986.

3. Tyrer, P., Rutherford, D., Huggett, T., Benzodiazepine Withdrawal Symptoms and Propranolol, Lancet 1:520-521, March 7, 1981.

4. Hollister, L.E., Clinical Pharmacology of Psychotherapeutic drugs, Churchill Livingstone, New York, 1978, pp. 41-42.

FDA/jaa