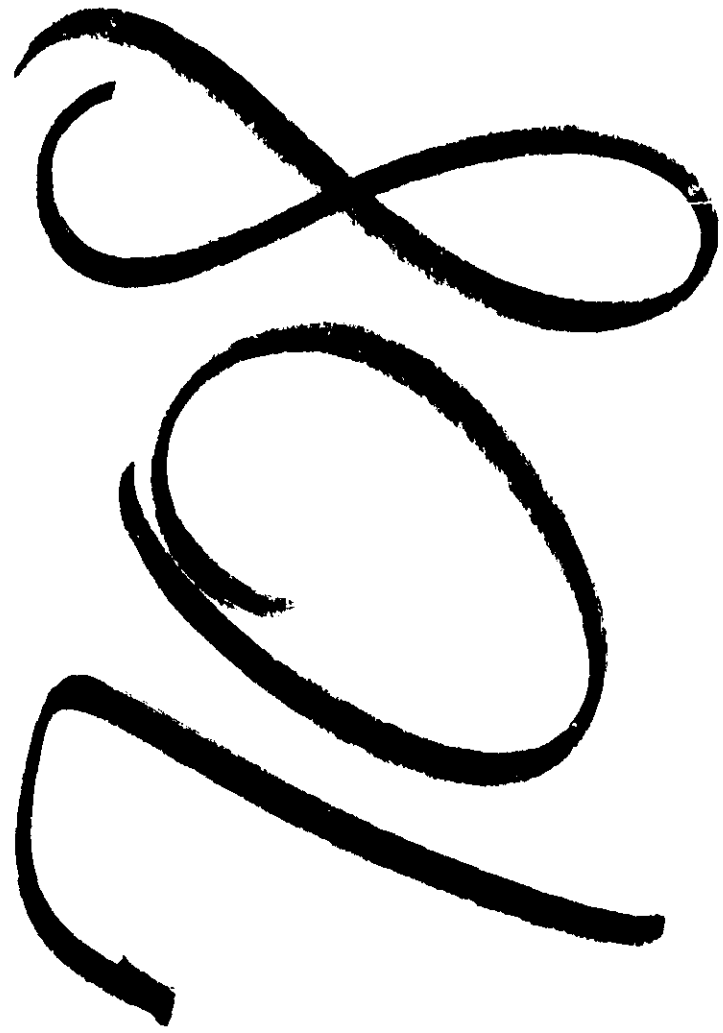


NDA 18-708

DEC 27 1985

Schering Corporation
Attention: Nelson H. Schimmel, M.D.
60 Orange Street
Bloomfield, New Jersey 07003

Dear Dr. Schimmel:

Please refer to your new drug application dated April 5, 1982, submitted pursuant to section 505(b) of the Federal Food, Drug and Cosmetic Act for Dormalin (quazepam) 15 mg tablets.

We also acknowledge receipt of your additional communications dated October 22, 1984, June 3 and September 5, 1985, and of your amendment dated November 25, 1985.

We have completed the review of this application, including the submitted draft labeling, and the application is approved, effective on the date of this letter. The changes agreed upon during a meeting on December 19, 1985, between representatives of Schering and this agency and listed in the addendum (q.v.), must be made in the labeling.

We also acknowledge your agreement to conduct the following studies in the postapproval period:

1. In your amendment dated November 25, 1985, you agreed to conduct an exploration of the applicability of aqueous buffers on solubilizing agents, and a study generating a pH-related dissolution profile. You agreed to use an ethanol media according to the parameters and specifications outlined in our letter dated August 30, 1985, until the revisions have been approved. We request that you submit the new information within 18 months.

2. In the meeting on December 19, 1985, you agreed to conduct a clinical study to evaluate the relationship between age and dose for quazepam. We request that you propose a design for an appropriate study for our review and comment within 12 months.

The labeling should be revised exactly as we have requested and twelve copies of the final printed version of the revised labeling (FPL) must be submitted to FDA prior to marketing. Marketing of the drug before the changes specified above are made and submitted to FDA, renders the product misbranded under 21 U.S.C. 352.

In addition, you may not legally market the drug until final rulemaking procedures for scheduling under the Controlled Substances Act are enacted by the Drug Enforcement Administration.

Should additional information relating to the safety and effectiveness of this drug product become available prior to our receipt of the final printed labeling, revision of that labeling may be required.

Please submit 12 copies of the revised final package insert and immediate container labels.

Also, please submit one market package of the drug which it is available.

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

Sincerely yours,

Robert Temple 12/2/85

Robert Temple, M.D.
Director
Office of Drug Research and Review
Center for Drugs and Biologics

Addendum: Final Labeling Draft

FINAL LABELING DRAFT

Addendum to approval letter for Dorwalin (quazepam) Tablets, NDA 18-708:

Note: Any text noted as acceptable refers to wording for the draft package insert submitted with Schering's letter dated November 25, 1985. The page numbers listed below refer to the pages of that attachment unless noted otherwise.

DESCRIPTION: Acceptable.

CLINICAL PHARMACOLOGY:

Central nervous system agents of the 1,4-benzodiazepine class presumably exert their effects by binding to stereo-specific receptors at several sites within the central nervous system (CNS). Their exact mechanism of action is unknown.

In a sleep laboratory study, quazepam significantly decreased sleep latency, total wake time, and significantly increased total sleep time and percent sleep time for one or more nights. Quazepam 15 mg was effective on the first night of administration. Sleep latency, total wake time, and wake time after sleep onset were still decreased and percent sleep time was still increased for several nights after the drug was discontinued. Percent slow wave sleep was decreased, and REM sleep was essentially unchanged. No transient sleep disturbance, such as "rebound insomnia", was observed after withdrawal of the drug in sleep laboratory studies in 12 patients using 15 mg doses.

The paragraph beginning "In out-patient studies" on Page 2 and the next two paragraphs on Page 3 are acceptable. The last sentence of the third paragraph on Page 3 should be deleted. The last paragraph on page 3 is acceptable.

The first paragraph on page 4 should be revised as follows:

The degree of plasma protein binding for quazepam and its two major metabolites is greater than 95%. The absorption, distribution, metabolism, and excretion of benzodiazepines may be altered in various disease states including alcoholism, impaired hepatic function, and impaired renal function.

The last two paragraphs on page 4 should be deleted and replaced by the standard labelling proposed on page 3-FDA of the approvable letter dated August 30, 1985. These paragraphs begin with "The type and duration of hypnotic effects" and end with "anxiety in selected patients".

The last paragraph under Clinical Pharmacology appearing at the top of Page 5 is acceptable.

INDICATIONS AND USAGE:

Quazepam is indicated for the treatment of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings. The effectiveness of quazepam has been established in placebo controlled clinical studies of five nights duration in acute and chronic insomnia. The sustained effectiveness of Quazepam has been established in chronic insomnia in a sleep laboratory (polysomnographic) study of 28 nights duration.

Because insomnia is often transient and intermittent, the prolonged administration of Dormalin (quazepam) is generally not necessary or 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 more specific treatment should be considered.

CONTRAINDICATIONS: Acceptable.

WARNINGS:

Patients receiving benzodiazepines should be cautioned about possible combined effects with alcohol and other CNS depressants. Also, caution patients that an additive effect may occur if alcoholic beverages are consumed during the day following the use of benzodiazepines for nighttime sedation. The potential for this interaction continues for several days following their discontinuance, until serum levels of psychoactive metabolites have declined.

Patients should be cautioned about engaging in hazardous occupations requiring complete mental alertness such as operating machinery or driving a motor vehicle after ingesting benzodiazepines, including potential impairment of the performance of such activities which may occur the day following ingestion.

The paragraph beginning "Withdrawal symptoms of the type" on page 4-FDA of the approvable letter dated August 30, 1985 should be incorporated as written.

PRECAUTIONS:

The three paragraphs in the General section listed on page 4-FDA and page 5-FDA of the approvable letter dated August 30, 1985 should be used with the following exceptions:

The first sentence of the first paragraph should state:

"Impaired motor and/or cognitive performance attributable to the accumulation of benzodiazepines and their active metabolites . . . ."

The first sentence of the first paragraph on page 5-FDA should state:

"When benzodiazepines are administered . . . ."

Information for Patients: It is suggested that physicians discuss the following information with patients. (This information to intended to aid in the safe and effective use of this drug. It is not a disclosure of all possible adverse or intended effects.)

Items 1 through 4 should be taken verbatim from those listed on page 5-FDA of the approvable letter dated August 30, 1985.

Item 5 should state:

"Benzodiazepines may cause daytime sedation, which may persist for several days following drug discontinuation."

Item 6 should state:

"Patients should be told not to increase the dose on their own and should inform their physician if they believe the drug does not work anymore."

Item 7 should state:

"If benzodiazepines are taken on a prolonged and regular basis (even for periods as brief as six weeks), patients should be advised not to stop taking them abruptly or to decrease the dose without consulting their physician, because withdrawal symptoms may occur".

Laboratory Tests: Acceptable.

Drug Interactions: Acceptable.

Carcinogenesis, Mutagenesis, etc.: Acceptable.

Teratogenic Effects: Acceptable.

Nonteratogenic Effects: Acceptable.

Labor and Delivery: Acceptable.

Nursing Mothers: Acceptable.

Pediatric Use: Acceptable.

ADVERSE REACTIONS:

Note: All of the text proposed in the Draft Labeling for the ADR section attached to the Schering letter dated November 25, 1985, up to the presentation of the table on Page 11, should be deleted and replaced by the following:

Adverse events most frequently encountered in patients treated with Dormalin are drowsiness and headache.

Accurate estimates of the incidence of adverse events associated with the use of any drug are difficult to obtain. Estimates are influenced by drug dose, detection technique, setting, physician judgments, etc. Consequently, the table below is presented solely to indicate the relative frequency of adverse events reported in representative controlled clinical studies conducted to evaluate the safety and efficacy of Dormalin. The figure cited cannot be used to predict precisely the incidence of such events during usual medical practice. These figures, also, cannot be compared with those obtained from other clinical studies involving related drug products and placebo.

The figures cited below are estimates of untoward clinical event incidences of 1% or greater among subjects who participated in the relatively short duration placebo-controlled clinical trials of Dormalin.

Insert the tables on Pages 11 and 12 with intervening text here.

The footnote at the bottom of Page 12 should be revised to include the following sentence:

"In addition, abnormalities in the following laboratory tests were observed in less than 1% of the patients evaluated: WBC count, platelet count, total protein, albumin, BUN, creatinine, total bilirubin, alkaline phosphatase, and SGPT."

After the footnote please follow with:

The following additional events occured among individuals receiving quazepam at doses equivalent to or greater than those recommended during its clinical testing and development. There is no way to establish whether or not the administration of Dormalin caused these events.

Hypokinesia, ataxia, confusion, incoordination, hyperkinesia, speech disorder, and tremor were reported.

Also, depression, nervousness, agitation, amnesia, anorexia, anxiety, apathy, euphoria, impotence, decreased libido, paranoid reaction, nightmares, abnormal thinking, abnormal taste perception, abnormal vision and cataract were reported.

Also reported were urinary incontinence, palpitations, nausea, constipation, diarrhea, abdominal pain, pruritus, rash, asthenia, and malaise.

Please delete the paragraph beginning "The following laboratory abnormalities".

The following list provides an overview of adverse experiences that have been reported and are considered to be reasonably related to the administration of benzodiazepines: incontinence, slurred speech, urinary retention, jaundice, dysarthria, dystonia, changes in libido, irritability, and menstrual irregularities.

As with all benzodiazepines, paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, hallucinations, and other adverse behavioral effects may occur in rare instances and in a random fashion. Should these occur, use of the drug should be discontinued.

There have been reports of withdrawal symptoms and signs 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 section).

DRUG ABUSE AND DEPENDENCE:

The text proposed in the approvable letter dated August 30, 1985, should be used except for the following modification in the first sentence:

"Withdrawal symptoms similar in character to those noted with sedative/hypnotics and alcohol have occurred following the abrupt discontinuation of drugs in the benzodiazepine class."

Controlled Substance Class: Acceptable.

OVERDOSAGE: Acceptable.

DOSAGE AND ADMINISTRATION:

Adults - Initiate therapy at 15 mg until individual responses are determined. In some patients, the dose may then be reduced to 7.5 mg (half of a scored tablet).

Elderly and debilitated patients - Because the elderly and debilitated may be more sensitive to benzodiazepines, attempts to reduce the nightly dosage after the first one or two nights of therapy are suggested.

HOW SUPPLIED: Acceptable.

Addendum (DOC#3741p)

Review and Evaluation of the Pharmacology and Toxicology Data and
Relevant Clinical Data of NDA 18-705
Drug Abuse Staff Consulting Review

Sponsor: Schering Corporation
60 Orange Street
Bloomfield, New Jersey 07003

Drug: quazepam

(7-chloro-5-(0-fluorophenyl)-1,3-dihydro-1-(2,2,2-trifluoroethyl(-2H-1,4-benzodiazepine)-2-5 thione.

Category: Benzodiazepine hypnotic agent

Background

Quazepam is a substituted 1,4 benzodiazepine agent which is seeking approval as a hypnotic agent. The clinical dosage form will be tablets of 15 and 30 mg strength. The indication is for the treatment of all types of insomnia, characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings. Quazepam is claimed to be effective in patients with recurring insomnia or poor sleep habits, acute or chronic medical situations requiring restful sleep, insomnia in geriatrics, and insomniac situations where fast onset is desirable. The sponsor believes that quazepam has a unique profile of effects and lacks substantive abuse liability. The sponsor's data and arguments, which are summarized in an April 14, 1983 submission for the Drug Abuse Advisory Committee meeting of April 28 and 29 of 1983, will be reviewed below. The sponsor's premise is that quazepam selectively stimulates a subset of benzodiazepine receptors which are responsible for sedation and sleep, but not a potential for abuse. The sponsor also claims that preclinical evaluations have demonstrated a long duration of action, less potential for ataxia, paradoxical excitation, and (less) tolerance than other benzodiazepines such as flurazepam.

On page 11 of the April 14, 1983 submission the sponsor has profiled the relative effects of quazepam and flurazepam in three different indications of sedative hypnotic potential in mice in Table 1. In general quazepam appears to be equipotent or slightly more potent than flurazepam in the test of hypnotic activity in mice. It should be noted that the LD_{50} of quazepam by mouth is greater than 5,000 mg/kg, suggesting an excellent therapeutic index. In terms of relative toxicity, quazepam is less toxic by mouth than chlordiazepoxide, diazepam, and temazepam. Flurazepam and oxazepam appear to be equitoxic to quazepam.

The squirrel monkey was the species chosen to study hypnotic effects of quazepam. Quazepam was approximately twice as potent in producing eyelid closure (a measure of sedation and hypnosis) than flurazepam. Flurazepam and quazepam were equipotent in producing ataxia. Thus, quazepam appears to produce less ataxia at equihypnotic doses.

Quazepam was also evaluated in the freely moving cat. Quazepam and flurazepam were equipotent in producing the behavioral effects (sedation and drowsiness), but flurazepam appeared to be more potent in terms of muscle relaxation and far more potent with respect to producing ataxia. Thus, in the cat, a dissociation between the sedative effect and the ataxic effect of quazepam has been demonstrated, whereas with flurazepam one would expect a greater degree of overlap. Further escalations of dose also revealed differences between flurazepam and quazepam. Quazepam produced increased drowsiness and sedation in all five cats tested up to 1,000 mg/kg, p.o. Flurazepam, on the other hand, produced stimulant effects at higher doses and all cats died at doses ranging from 250 to 600 mg/kg, p.o. Acute lethality data in the cat suggest that quazepam has less acute toxicity than flurazepam. Given that quazepam and flurazepm are approximately equipotent with respect to sedation and hypnosis in the cat, this suggests that quezepam has a good margin of safety in the cat.

Other data obtained in both mice and cats appears to substantiate the differences observed betwen quazepam and flurazepm with respect to "paradoxical" excitation. In the mouse, quazepam produces a dose-related suppression of locomotor activity, whereas flurazepam incrases locomotor activity in doses up to 5 mg/kg. EEG studies in immobilized cats also support the difference with respect to paradoxical excitation. Following quazepam administration, the EEG is consistent with sedation, showing slow wave and spindle activity, whereas the EEG following quazepam administration snows beta activity, suggesting a stimulatory component to the action of flurazepam.

Quazepam was tested for reinforcing properties in an intragastric self-administration model in the rhesus monkey. These data are presented in Table 5 on page 20 of the sponsor's submission. The data show that only 2 of 4 monkeys initiated self-administration at the unit dose of 0.25 mg/kg. When higher doses, 1 to 4 mg/kg were tested, the 2 monkeys who did not self-administer at the 0.25 dose also failed to administer at the higher doses. The 2 monkeys who self-administered at the 0.25 mg/kg dose administered less quazepam at the unit doses of 1 and 4 mg/kg. Animals received 2 weeks of programmed administration of the drug at 1 mg/kg every 4 hours daily for 2 weeks. Even following this manipulation, the self-administration of doses in the 0.25 to 4 mg/kg range was marginal. These results may be best appreciated when compared to a standard drug in this intragastric self-administration paradigm. Yanagita and Cato reported on the intragastric self-administration of diazepam in the monkey. (Presented at the CPDD meeting in Toronto in 1982). A dose of diazepam 0.25 mg/kg increased rate of responding (over

saline control) in 2 of 4 monkeys. At a dose of 1 mg/kg, responding was maintained above the original vehicle level in only 1 of 4 subjects and only this subject retained relatively high levels of drug intake when the dose was again set at 0.25 and, subsequently, reset to 1 mg/kg. When a vehicle probe was inserted for three days, the animal showed rates of responding higher than originally maintained by vehicle in 2 of 4 subjects. Further unit doses of 1 and 2 mg/kg of diazepam did not increase intake appreciably above vehicle level. A final return to a vehicle probe for 1 one week generally resulted in levels of responding that were comparable to the second determination of vehicle levels and greater than the levels of vehicle maintained initially. Although the results of this study indicate intragastric diazepam was self-administered by the rhesus monkey, the effect is weak-to-modest at best. Moreover, the self-administration of diazepam and quazepam show few, if any, relevant differences in the intragastric self-administration model. Furthermore, the results obtained in the intragastric self-administration model in the rhesus monkeys are probably representative of benzodiazepine self-administration paradigms in general. Griffiths and Ator (1981) reported that benzodiazepine self-administration studies show these drugs to be considered moderately reinforcing. These authors concluded that benzodiazepines as a class are more efficacious as reinforcers than chlorpromazine, imipramine, haloperidol or Perphenazine, but were clearly less efficacious than amobarbital, secobarbital, alcohol, or cocaine. (Griffiths, R.R. and Ator, N.A. in Benzodiazepines, S.I. Szara, and J.P. Ludford (Eds.), NIDA Research Monograph 33, U.S. Government Printing Office, Washington, D.C., page 22-36, 1981.

The sponsor had indicated that the self-administration profile of quazepam is similar to halazepam. Thereafter the sponsor discusses the differential selectivity of both quazepam and halazepam for BZ_1 receptors. It has been reported by Jaffe, et al, (1983) that halazepam is substantially less euphoric than diazepam. The sponsor then develops an analogous argument that quazepam should have substantially less psychological dependence capacity. However, in the monkey, the self-administration profile of quazepam is also similar to diazepam (vide supra). Thus, the selective or relatively selective affinity for one receptor subtype over another has not been correlated with a reinforcement or lack of reinforcement effect. Thus, the sponsor's analogous reasoning is faulty and the sponsor has not demonstrated any less liability for psychological dependence than diazepam.

Tables 6, 7 and 8 (of the sponsor submission) illustrate the preference of halazepam and quazepam for the "BZ_1 receptor." The "BZ_1" receptor density is highest in the cerebellum and the "BZ_2" type receptor occurs with greater prevalence in the hippocampus. Although I am in agreement with the sponsor's analysis that quazepam has preferential affinity for the "BZ_1" receptor, it is only speculation as to whether this confers unique properties onto quazepam; i.e., a lack of abuse.

The next section of the sponsor's report deals with issues of tolerance and physical dependence. The sponsor has demonstrated in Figure 5 that quazepam pretreated mice do not develop tolerance to the anticonvulsant effect of quazepam, whereas flurazepam-treated mice demonstrate tolerance. It should be noted that tolerance development to a specific effect does not imply that a global tolerance to all drug effects are occurring. It should be appreciated that the lack of tolerance to one effect does not imply that tolerance can not develop to another effect. It should also be noted that tolerance is neither a necessary nor a sufficient condition for physical dependence to occur. The role of tolerance in the maintenance of drug-seeking behavior in drug-abusing populations is severalfold:

1. It shortens the duration of action and decreases potency of drugs, necessitating an increased amount of drug and shorter inter-drug ingestion or injection intervals; (This has implications in terms of both operant and classical conditioning effects).

2. It can magnify the appetitive effects of a drug due to tolerance development to aversive effects (e.g., vomiting

3. It may confer additional safety to a drug in a drug-abusing population; that is, there may be fewer overdoses in an abusing population per dose as opposed to a drug-naive population.

The physiologic dependence capacity of quazepam has been studied in rhesus and squirrel monkeys. In rhesus monkeys, increasing doses of quazepam were administered to 5 monkeys over a five-week period. Abrupt withdrawal was performed at the beginning of the fifth week. Mild withdrawal signs were seen in 3 of 5 monkeys (apprehension, hyperirritability, mild tremor, anorexia, and piloerection) and intermediate withdrawal signs were seen in 2 of 5 monkeys (aggravated tremor, muscle rigidity, impaired motor activity, retching or vomiting, or weight loss of 10%). It should be noted that the aforementioned signs designate the differentiation of mild and intermediate withdrawal. They are not necessarily observed in every monkey. Quazepam was again administered for four weeks, the highest dose being 64 mg/kg/day. At the beginning of the 10th week, a second withdrawal period was initiated. There was a slight increase in withdrawal severity with 3 of 5 having intermediate withdrawal signs and 2 of 5 monkeys having mild withdrawal signs.

Quazepam was tested for substitution capacity in a barbital-dependent rhesus monkey model. Quazepam produced incomplete suppression of withdrawal at 4 mgs and complete suppression of withdrawal in 2 to 4 monkeys at 8 and 16 mg/kg. For comparison, flurazepam at 16 mg/kg also produced complete suppression in 2 of 4 monkeys.

The physical dependence capacity of quazepam was also studied in squirrel monkeys. Quazepam doses of 2, 5 or 50 mg/kg was administered for 52 weeks. An additional group received diazepam, 50 mg/kg. The highest doses of quazepam and diazepam are approximately 83 and 63 times the usual therapeutic

daily doses, respectively, (based on mg/kg comparisons between man and monkey). Dose and drug-related sedation, somnolence, ataxia and tremors were observed. The frequency was greatest during the first three weeks of dosing. During the first week of the study, several high-dose quazepam- and diazepam-treated monkeys were unable to move without falling. Following the last doses of quazepam and diazepam, animals were observed for withdrawal signs. Ataxia, emesis, tremors, and convulsions occurred within 3 days of cessation of dosing. Convulsions lasted a few minutes, and were followed by either complete recovery or death. One monkey found convulsing was given diazepam and appeared normal 20 minutes later. Three days later the animal convulsed and died several days later.

The dose-time relationships and comparative physical dependence capacity of benzodiazepines are poorly understood. The data in the rresus monkey on quazepam are not comparable to other data derived even in the same laboratory. For comparison purposes, the animals would have to have been put on a chronic equivalent dosing regimen similar to that described by Boisse and Okamoto, 1978 (see Boisse, N.R. and Okamoto, M., J. Pharmacol. Exp. Ther., Vol. 204: 497, 1978). To my knowledge, the only comparative benzodiazepine physical dependence study on record is the Schering study with quazepam and diazepam in the squirrel monkey. Thus, there is not enough background information to judge the validity of this model in terms of the relevance to physical dependence in the human. It should be noted that this study utilized high doses of quazepam and diazepam administered for a long period (52 weeks). The severe convulsions and lethality which occurred in both the quazepam and diazepam groups have not been observed in other models of benzodiazepine physical dependence. It should be noted that convulsions have been reported in patients withdrawing from benzodiazepines. However, no lethalities have been reported for benzodiazepine withdrawal syndromes.

The sponsor has added a section which overviews the clinical studies with quazepam. Table 14 gives a distribution of adverse reactions as a function of treatment. It should be noted that although the quazepam side effect incidence appears to be less than for flurazepam, the dose levels are not mentioned. Thus, it may be that the combined 15 and 30 mg dosage data on quazepam may have lesser side effects than that seen with flurazepam. I have one other comment about the clinical studies. Table 21 illustrates that in studies of between 4 and 18 nights there was essentially no REM rebound during the post-drug period. This would be expected given a drug with a long half-life of elimination.

The sponsor has also a provided a summary of the metabolic and pharmacokinetic data on quazepam. Of particular interest is the fact that quazepam is rapidly absorbed with a peak plasma concentration occuring between 1 and 2 hours. The terminal half-life of quazepam and 2-oxoquazepam are fairly long, being 39.3 and 40.2 hours as reported in Figure 1, respectively. Additionally, N-desalkylflurazepam, an active metabolite with a terminal elimination

half-life of 69.5 hours has also been noted. The pharmacokinetics of quazepam may bear on the abuse potential of the substance. It has been suggested that the reinforcing properties of rapidly absorbed benzodiazepines may increase their abusability, in that person's using these drugs for pleasure-seeking may select those which are rapidly absorbed. (See Stitzer, et al, Drug and Alcohol Dependence, Vol. 8., page 189, 1981; Griffiths and Ator, 1981). Jasinski, et al (1981) reported that 10, 20 and 40 mg of diazepam produced pentobarbital like euphoria with a time course similar to pentobarbital. See Jasinski, D.R., Haertzen, J.E., Henningfield, R.E., Johnson, R.E., Makhzoumi, H.M., Miasato, K. reported to Committee on Problems of Drug Dependence, 1981). Griffiths, et al, 1980 administered diazepam and pentobarbital to sedative hypnotic abusers over a wider dose range. The results suggest a flatter dose response for diazepam as only modest elevations of subject liking were recorded for diazepam, and pentobarbital was consistently preferred. The results also suggest that euphoria inhibiting effects of residual benzodiazepine levels may affect liking scores and drug preference in a chronic administration paradigm. Diazepam and desmethyldiazepam have fairly long elimination half-lives, thus possibly limiting the amount of receptor stimulation seen in chronic dosing situations. This could reduce the amount of CNS effect perceived and result in a diminution of the liking score. Quazepam has not been tested in a self-administration paradigm in sedative-hypnotic abusers. It would be my prediction that quazepam would have a liking score similar to pentobarbital in a Jasinski model, and similar to diazepam in a Griffiths model. At any rate, the sponsor could test for differences in liking scores in either or both models and possibly demonstrate whether there really is a difference in the magnitude or time course of the liking scores which could translate to a difference in abuse potential.

The dependence potential of quazepam has to be viewed from at least two perspectives. The first perspective is whether or not a patient population would become dependent on quazepam. At this time data do not exist to answer the question. Quazepam should be administered to a group of insomniacs who are allowed to freely dose for a given period of time. The drug should be compared to a known standard and possibly also to placebo. The amount of time that subjects stay on quazepam as opposed to the active control and placebo and the preference of quazepam to the other two drugs might give a better indication of the drug's abuse potential in a chronic patient population. The second concern would be a concern of actual physical dependence in both a patient population and a drug abusing population. Obviously, one might be more concerned with a drug abusing population since they would likely abuse the drug at higher doses. The dose-time relationships for physical dependence attainment for any benzodiazepine have not been worked out. Thus, I can only speculate as to whether or not quazepam would produce physical dependence in a patient population. To date, studies suggest that clinical doses, i.e. up to 30 mg a night for 4 weeks, do not produce a significant withdrawal syndrome. However, therapeutic dosing for longer than four months or more or increases in dose might increase the incidence of withdrawal reactions. It would seem

prudent to allow that gradual tapering of the dose should occur to minimize the possibility of withdrawal emergence.

Conclusions:

The sponsor has not demonstrated that quazepam is significantly different from other benzodiazepines with respect to abuse potential. Available behavioral and biochemical data in animals suggest that quazepam may selectively stimulate a benzodiazepine type I receptor. However, whether this will correlate with a reduced abuse potential is unknown at this time. The physical dependence properties of quazepam cannot be compared to any known benzodiazepine or other sedative-hypnotic. However, it can be stated with some degree of certainty that physical dependence can be produced with high doses given over a fairly long period of time. Additional studies could evaluate the dose-time relationships involved in determining the dependence potential of quazepam.

The pharmacokinetic data demonstrate that quazepam is rapidly absorbed and has active metabolites with long half-lives. Assuming a correlation between rate of drug rise in plasma and CNS depression, these data suggest that quazepam would produce rapid sedation. This property indicates a potential for abuse similar to other Schedule IV benzodiazepines. The long half-lives of quazepam and its metabolites might decrease dosing in a chronic situation; such an observation has been made by Griffith, et al., 1980 in a population of sedative-hypnotic abusers who were chronically administering diazepam. Methodologies exist to test both the single and chronic subjective effects of quazepam vis-a-vis halazepam and diazepam. I would recommend that such a study be done if the sponsor wants to demonstrate a difference in abuse potential between diazepam and quazepam.

Recommendation:

Quazepam should be placed in Schedule IV of the Controlled Substances Act if and when quazepam is approved for marketing.

Frank J. Vocci Jr., Ph.D.
Frank J. Vocci, Jr., Ph.D.

cc:
Orig. NDA
HFN-220
HFN-120
HFN-123/FVocci/4/21/83
Edit:FVocci/4/26;4/28/83
FT/dcm:4/22/83/lca:4/26/83
RD/dcm/4/27;4/28/83
DOC# 5837B

Robert Hollenbeck, Ph.D.
June 3, 1985

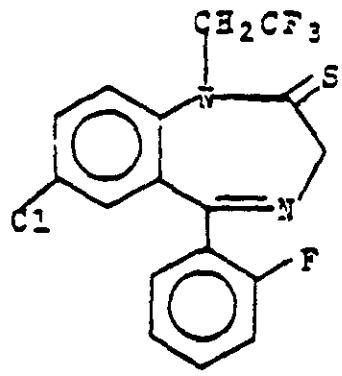
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
ORIGINAL SUMMARY NDA 18-708

Sponsor: Schering Corporation
Bloomfield, New Jersey

Drug: Quazepam

Category: hypnotic

Chemical Structure:



Chemical Names:

1) 7-Chloro-5-(2-fluorophenyl)-1,3-dihydro-1-(2,2 2-trifluorophenyl)-2H-1,4-benzodiazepine-2-thione

2) 7-Chloro-5-(o-fluorophenyl)-1,3-dihydro-1-(2,2,2-trifluorophenyl)-2H-1,4-benzodiazepine-2-thione

Drug Code Number: SCH 16134

Trade Name: not yet available

Formulation: Tablets of 15 and 30 mg Quazepam

Proposed Clinical Indication:

For the treatment of all types of insomia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings. Quazepam is claimed to be effective in patients with recurring insomnia or poor sleep habits, acute or chronic medical situations requiring restful sleep, insomnia in geriatrics, and insomniac situations where fast onset is desirable.

Preclinical Studies and Testing Laboratories:

Except for a mouse reproduction study which was performed by Huntingdon Research Centre, U.K., the testing of quazepam was conducted at Schering Corporation, Department of Pathology and Toxicology. Tables showing types of studies performed, results obtained and descriptive material, were prepared by the sponsor and have been included in several parts of this review.

Relationship to Other Chemically and Pharmacologically Related Drugs:

Quazepam is a hypnotic agent which is related to flurazepam and diazepam. It is a 1,4-benzodiazepine derivative containing a trifluoroethyl, sulfur, and aryl group in the first, second, and fifth positions, respectively.

QUAZEPAM

Table of Contents

Table 1. - TOXICOLOGY AND PATHOLOGY (PRECLINICAL) EXAMINATIONS OF QUAZEPAM

Species	# Males	# Females	# Animals/ Group	Study Design	Study Duration	Quazepam Daily Dosage	Route of Administration	Dosage Form
Mouse	20	20	20	Acute	2 wks (single administration)	0,5000 mg/kg	Oral (esophageal intubation)	suspension
	70	60	10[a]	Acute	2 wks (single administration)	0,525,603,695, 795,845,893,915, 945,1000,1050, 1060 mg/kg	Intraperitoneal injection	suspension
	80	80	40	Subacute	13 wks	0,5,25,100[b] mg/kg	Oral (esophageal intubation)	suspension
	40	40	40	Subacute	13 wks	0,50 mg/kg	Oral (esophageal intubation)	suspension
	75	150	45	Segment I	F_0: 16 wks F_1: 16 wks	0,6,18,54 mg/kg 54 mg/kg-diazepam	Oral (gavage)	suspension
	-	125	25	Segment II	3 wks	0,3,20,120 mg/kg 160 mg/kg-diazepam	Oral (esophageal intubation)	suspension
	-	125	25	Segment III	6 wks	0,3,9,18 mg/kg 18 mg/kg-diazepam	Oral (esophageal intubation)	suspension
	-	100	25	Segment III	6 wks	0,9,18 mg/kg 18 mg/kg-diazepam	Oral (esophageal intubation)	suspension
	240	240	60[c]	Oncogenicity	79-91 wks	0,30,60,120 mg/kg	Oral (diet)	bulk (powder)

[a] - 20 vehicle control mice/group
[b] - Treatment terminated at week 3
[c] - 240 control mice/group

Table 1. - TERATOLOGY AND FERTILITY INCLUSION, INHIBITIONS OF QUAZEPAM

Species	# Males	# Females	# Animals/ Group	Study Design	Study Duration	Quazepam Daily Dosage	Route of Administration	Dosage Form
Rat	20	20	20	Acute	2 wks (single administration)	0,5000 mg/kg	Oral (esophageal intubation)	suspension
	50	60	20	Acute	2 wks (single administration)	0,2000,2520, 3160,3900, 5000 mg/kg	Intraperitoneal injection	suspension
	70	-	10	Acute	2 wks (single administration)	0,1250, 2500, 5000 mg/kg 1250,2500, 5000 mg/kg-SQH 15725	Oral (esophageal intubation)	suspension
	90	70	8 to 12	Acute	2 wks (single administration)	0, 1000 mg/kg	Oral (gavage)	suspension
	20	20	10	Subacute	3 wks	0,50,100, 200 mg/kg	Oral (diet)	bulk (powder)
	-	110	25[d]	Segment II	3 wks	0,25,50, 100 mg/kg	Oral (esophageal intubation)	suspension
				Subacute (Pilot)	5 wks	0,125,250, 500 mg/kg	Oral (diet)	bulk (powder)
Hamster	40	40	16[e]					
	216	216	72[f]	Chronic	52 wks	0,3,20,120 mg/kg 120 mg/kg-diazepam	Oral (diet)	bulk (powder)
	336	336	112[g]	Carcinogenicity	57-79 wks	0,3,20,120 mg/kg 120 mg/kg-diazepam	Oral (diet)	bulk (powder)

d - 35 vehicle control females/group
e - 32 control hamsters/group
f - 144 control hamsters/group
g - 224 control hamsters/group

Table I. - TOXICOLOGY AND PATHOLOGY PRECLINICAL INVESTIGATIONS OF QUAZEPAM (Cont'd.)

Species	# Males	# Females	# Animals/ Group	Study Design	Study Duration	Quazepam Daily Dosage	Route of Administration	Dosage Form
Rabbit	-	58	14[f]	Segment II	4 wks	0,10,20,40 mg/kg	Oral (esophageal intubation	suspension
Dog	1	1	2	Acute	3 wks	1000 mg/kg	Oral	capsule (powder)
	1	2	2[h]	Dose Range	6 wks	0,50,100,200, 400,800,1600 mg/kg	Oral	capsule (powder)
Monkey	13	15	6[i]	Subacute	13 wks[i]	0,2,10,50,50[i] mg/kg	Oral (gavage)	suspension
	25	25	10	Chronic	56 wks	0,2,10,50 mg/kg 50 mg/kg-diazepam	Oral (gavage)	suspension
Cat	-	10	5	Dose Range	approx. [g] up to 7 wks	0.1-1000 mg/kg 0.1-600 mg/kg-flurazepam	Oral	capsule (powder)

[f] - 16 vehicle control rabbits/group
[g] - 4 weeks post-treatment included
[h] - 1 control female dog
[i] - An additional group of four high-dose monkeys were evaluated for post-treatment effects for 20 days following a 13-week dosing period.

NCA 18-708

Pharmacology Synopsis

	Test	Drug	Route	ED_{50}(mg/kg)
(1)	potentiation of hexobarbital-induced sleeping time in mice	quazepam	p.o.	2.7
		flurazepam	p.o.	3.9
		diazepam	p.o.	1.0
(2)	antagonism of electroshock (13mA,60Hz) induced convulsions in mice	quazepam	p.o.	0.9
		flurazepam	p.o.	1.6
		phenobarbital	p.o.	5.6
(3)	antagonism of isolation-induced agression in mice	quazepam	i.p.	10.7
		flurazepam	i.p.	40.0
		diazepam	i.p.	8.7
(4)	antagonism of footshock-induced fighting-in mice (0.5mA)	quazepam	p.o.	1.5
		flurazepam	p.o.	1.5
		diazepam	p.o.	1.5
(5)	antagonism of metrazol-induced seizures in mice	quazepam	p.o.	0.3
		flurazepam	p.o.	1.7
		diazepam	p.o.	0.3

Quazepam was found to be twice as potent as flurazepam and half as potent as lorazepam as a hypnotic as measured using the eye-closure test in monkeys. Some of the above-mentioned tests are used to evaluate the drugs potential as a tranquilizer or an anticonvulsant even though this compound is to be marketed as a hypnotic. The main behavioral effect of the drug in animals was drowsiness and sedation. While many benzodiazepines produce a stimulant effect in the cat, quazepam showed a depressant effect in this species. Studies of the dependence potential of quazepam produced results which suggested a similar profile to that of marketed benzodiazepines. Like diazepam and flurazepam, quazepam potentiated the ethanol-induced loss of righting reflex in mice. One study showed evidence that the hypnotic effect of quazepam may be potentiated by propranolol or alpha-methyldopa. Quazepam produced no significant changes in blood pressure, heart rate, or EKG in the unanesthetized dog when doses (60 mg/kg) large enough to cause ataxia and sedation were used. The four identified metabolites of quazepam produce in the mouse effects which are similar to those of the parent compound both quantitatively and qualititatively, namely, decreased motor activity, increased passivity, decreased muscle tone, decreased visual placing reflex, ataxia, and impairment of righting reflex. The rat was insensitive to quazepam due to rapid metabolism and excretion of the compound in that species. (see below).

SELECTION OF ANIMAL SPECIES FOR LONG TERM TOXICOLOGY STUDIES WITH QUAZEPAM

Pharmacological screening test showed quazepam to be largely inactive in the rat and toxicity studies using doses up to 5000 mg/kg, p.o., or a single dose to Charles River CD rats produced no evidence of toxicity (report P-4287, Schering). A further study showed that daily oral doses of 200 mg/kg for 21 days in the rat elicited no observable effects. To test whether the effect was strain-related, another study (#5003) was performed using eight strains of rat each receiving 1000 mg/kg of drug. Some ataxia and sedation was observed, but the effect was not markedly different among the strains. The observation that quazepam was virtually inactive pharmacologically in the rat came during a study of sedative-hypnotic activity of the drug in a series of accepted tests using either mouse or rat. The series of tests included (study P-4159) hexibarbital potentiation in mice, antagonism of metrazol-induced seizures in mice, taming action in fighting mice, isolation-induced aggression in mice, blockade of mouse-killing (muricide) behavior in rats, conflict procedure in rats, and prevention opiate-induced rigidity in rats. The latter three studies using rats demonstrated only minimal activity of quazepam when compared with similar doses of flurazepam and diazepam. These studies as well as the lack of toxicity of quazepam when given orally to the rats in doses greater than 5000 mg/kg led to the conclusion that the rat would not be a suitable model for long term toxicity testing with quazepam.

In a study comparing absorption, tissue distribution, and excretion of labeled quazepam in rat and mouse (P-4307) the sponsor found that in the rat, quazepam is well absorbed by the oral route but is metabolized and excreted so quickly at tissue levels of drug needed to produce pharmacological effects are not achieved. Thus the rat was found unsuitable for long term toxicity study of quazepam. The hamster was selected for long term studies since that species showed pharmacologic and toxicologic responses to quazepam administration. ADME studies in the hamster further showed metabolic treatment of quazepam in that species to be similar to that found in man (study P-4785).

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Absorption, Distribution, Metabolism, Excretion

Drug metabolism, etc. of quazepam was studied in the mouse, rat, hamster, and squirrel monkey after both oral and i.v. administration. The sponsor has provided an accurate summary of the study data, and this summary is included on the following several pages as part of this review.

Drug Metabolism

Synopsis

The absorption, tissue distribution, metabolism and excretion (ADME) of ^{14}C- and/or ^{3}H-quazepam were evaluated in the mouse, rat (pilot study), hamster and squirrel monkey after single oral and intravenous administration.

The metabolic / pharmacokinetic data of quazepam are described for the mouse, hamster, squirrel monkey and man (for comparative purposes only) in Table 1. The excretory (Table 2) and metabolic (Table 3) profiles in animals (mouse, hamster, squirrel monkey) and man are given. The postulated major metabolic pathways are presented in Figure 1.

The major conclusions based upon all studies conducted are:

- Quazepam (orally) is well absorbed by all species studied.
- Quazepam is almost totally metabolized and first pass metabolism is extensive in all species (mouse, hamster, squirrel monkey, man) evaluated. Quazepam's metabolic pattern in these species is qualitatively similar. The metabolites: Sch 15725, Sch 17514, Sch 23309, Sch 23324 are pharmacologically active.
- The plasma half-lives of quazepam and its metabolites vary between species: The shortest half-lives occurred in mouse and hamster, and the longest half-lives were in squirrel monkey and man.

- Quazepam and its metabolites are widely distributed throughout the tissues (mouse, hamster). For most tissues the concentrations of radioactivity are similar to those in plasma. All tissue radioactivity decreased with time and no tissue drug accumulation occurred
- Quazepam penetrates the placental barrier more readily at near-term (day 18 of pregnancy) than at the end of embryonic formation (day 12). At 18 days, the concentration of radioactivity in fetal tissues are lower than corresponding maternal tissues. Radioactivity disappears at the same rate in the fetus and dam. Radioactivity did not accumulate in fetal tissues. The metabolic profile of quazepam in fetal tissues and maternal plasma was qualitatively similar.
- Quazepam and its metabolites (Sch 15725, Sch 17514, Sch 23309, Sch 23324 and other unidentified metabolites) are excreted in urine and feces, mostly within the first 24 hours after drug administration. A major portion of the quazepam dose (oral, intravenous) is excreted into the urine by the hamster, and into the feces by the mouse; while the squirrel monkey excreted almost the total dose into the feces.
- In mice, quazepam is not an inducer of hepatic drug metabolizing enzyme systems; in hamsters quazepam has only weak induction properties.

- In the rat, the radioactive dose is rapidly and completely absorbed, totally metabolized, and subsequently eliminated very rapidly (mostly in the bile). The resulting very low plasma levels may explain the lack of pharmacologic activity observed in this species.
- The metabolism and excretion pattern of quazepam is similar after intravenous and oral administration.

Table 1. Preclinical metabolic/pharmacokinetic studies with single oral doses of ^{14}C-quazepam.

Pharmacokinteic parameters	Mouse	Hamster	Squirrel Monkey	Man[a]
	(5 mg/kg)	(5 mg/kg)	(10 mg/kg)	(0.4 mg/kg)[b]
Plasma				
Radioactivity				
Tmax (hrs)	1.0	0.5	16.0	1.8
Cmax (ng equiv./ml)	722.8	988.0	2161.0	324.6
$t_{\frac{1}{2}}$ (hrs)	17.8	35.3	43.0[c]	75.6
AUC (ng hr/ml)[d]	6261.8	12467.5	73011.0	11402.3
Quazepam (Sch 16134)				
Tmax (hrs)	0.5	0.25	2.0	1.5
Cmax (ng/ml)	10.1	28.0	34.0	148.0
$t_{\frac{1}{2}}$ (hrs)	1.2	2.4	10.0[c]	39.3
AUC (ng hr/ml)[d]	18.2	24.8	300.0	714.6
2-Oxoquazepam (Sch 15725)				
Tmax (hrs)	0.5	0.25	2.0	1.6
Cmax (ng/ml)	13.2	99.6	41.0	45.6
$t_{\frac{1}{2}}$ (hrs)	1.6	1.9	13.0[c]	40.2
AUC (ng hr/ml)[d]	34.5	49.6	470.0	438.3
N-Desalkylflurazepam (Sch 17514)				
Tmax (hrs)	1.0	0.5	16.0	14.0
Cmax (ng/ml)	219.4	83.6	1416.0	40.9
$t_{\frac{1}{2}}$ (hrs)	1.2	0.6	43.0[c]	69.5
AUC (ng hr/ml)[d]	518.2	107.7	46390.0	3323.4

a = Given for comparative purposes only.
b = 25 mg in an alcoholic solution per subject.
c = approximate value.
d = AUC's are for up to 24 hours for mouse and hamster, 168 hours for squirrel monkey and 120 hours for man.

Table 2. Excretory profile of radioactivity after single doses of ^{14}C-quazepam in animals and man.

Specimen	Percent of Dose Excreted						
	Mouse		Hamster		Squirrel Monkey		Man[a]
	(4 days)		(7 days)		(7 days)		(5 days)
	p.o. (5 mg/kg)	i.v. (5 mg/kg)	p.o. (5 mg/kg)	i.v. (1 mg/kg)	p.o. (10 mg/kg)	i.v. (1 mg/kg)	p.o. (0.4 mg/kg)
Urine	36.6	42.9	53.8	57.3	1.0	1.0	31.3
Feces	61.5	56.9	43.0	40.1	84.0	79.4	22.7
Total	98.1	99.8	96.8	97.4	85.0	80.4	54.0

a = Given for comparative purposes only.

Table 3. Comparative metabolic pattern (relative abundance)[a] of ^{14}C-quazepam in the 24-hour urine (mouse, hamster, man) and 24-hour feces (squirrel monkey).

Compounds*	Mouse	Hamster	Squirrel Monkey	Man[b]
Sch 16134 (Quazepam)	Tr	Tr	Tr	Tr
Sch 15725 (2-Oxoquazepam)	Tr	Tr	+	+
Sch 23324 (3-Hydroxy-2-oxoquazepam)**	+	++	++++	++++
Sch 17514 (N-Desalkylflurazepam)	+	+	+	++
Sch 23309 (3-Hydroxy-N-desalkylflurazepam)**	+++	+++	+	++
Non-identified polar material	++++	+++	+	+

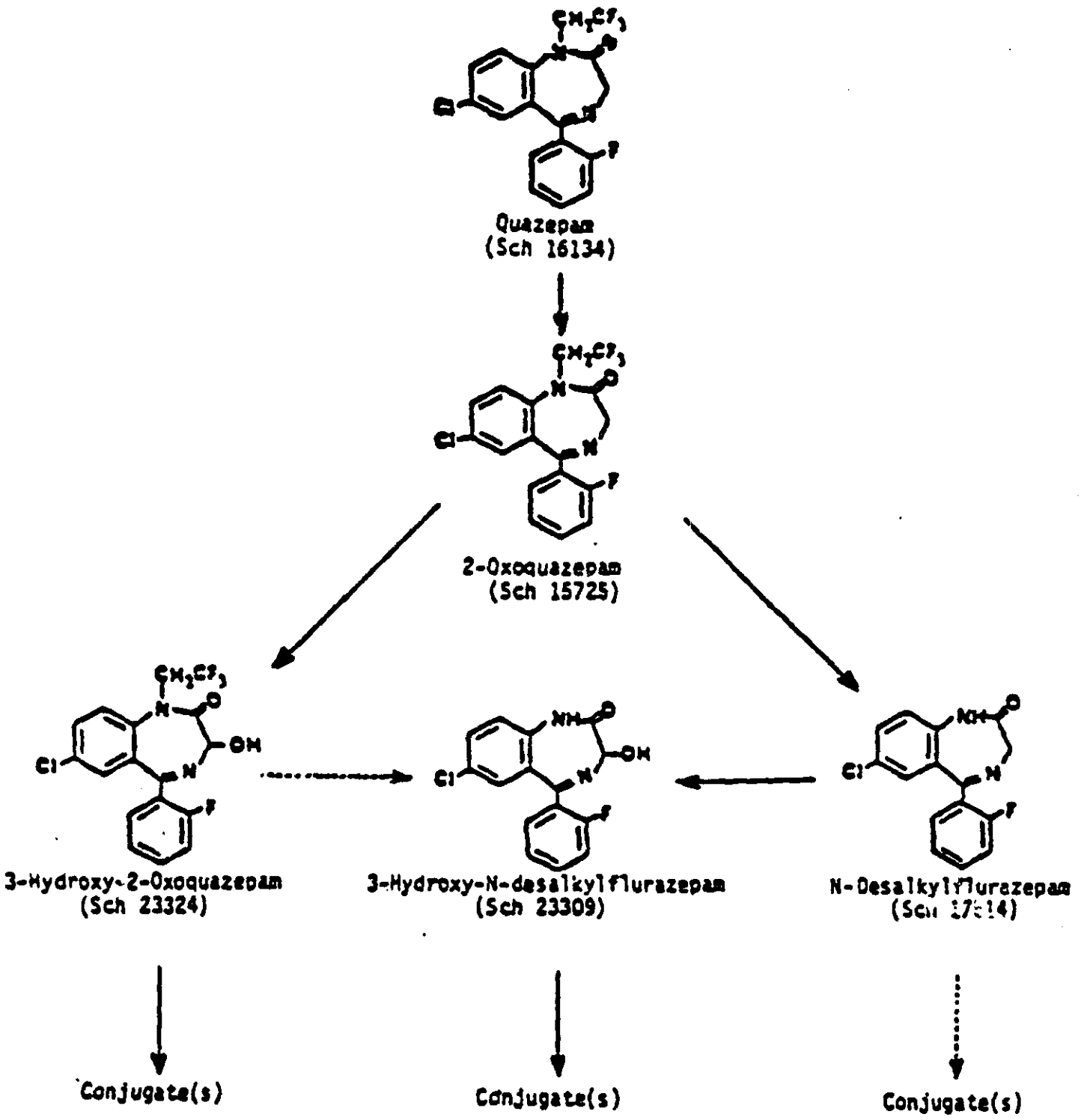
* See structures in Fig. 1.

** Free and conjugated.

a = Tr (trace) ⟶ + (minor) ⟶ ++++ (major)

b = Given for comparative purposes only.

Figure 1. POSTULATED MAJOR METABOLIC PATHWAYS



Preclinical Metabolic Studies: Mouse, Rat, Hamster, Squirrel Monkey

The absorption, tissue distribution, metabolism and excretion of ^{14}C-quazepam were studied in the mouse, hamster and squirrel monkey following single oral and intravenous dosing. These species were selected for metabolic evaluation since they had been used for pharmacologic testing and toxicologic evaluation of quazepam. A pilot study was done in the rat evaluating absorption, tissue distribution and excretion of ^{3}H-quazepam. Additional studies evaluated placental transfer (mouse) and drug induction (mouse, hamster) of quazepam.

In these studies, the concentrations of radioactivity in plasma, urine, feces and other biological specimens were determined by liquid scintillation spectrometry. The concentrations of unchanged quazepam and two metabolites (2-oxoquazepam = Sch 15725; and N-desalkylflurazepam = Sch 17514) in plasma were determined by specific and sensitive gas-liquid chromatographic (GLC) methods. The metabolic profile of quazepam was determined by thin-layer chromatography (TLC). The identified metabolites: Sch 15725, Sch 17514, Sch 23309, Sch 23324 have been shown to be pharmacologically active.

1) Mouse

Method

The absorption, tissue distribution, metabolism and excretion of quazepam were studied in 90 (fifteen groups of 6 animals each) male CD-1 albino mice (20 to 25 grams) following single oral (p.o.) and intravenous (i.v.) dosing with ^{14}C-quazepam (5 mg/kg).

Absorption

^{14}C-quazepam absorption in mice was rapid and at least 85% complete based upon plasma radioactivity levels (oral) and excretion (oral, intravenous) data.

Mean peak plasma concentrations of radioactivity (723 ng quazepam equiv./ml) occurred 1.0 hour after oral dosing; thereafter, the plasma radioactivity declined with an elimination half-life of approximately 18 hours.

Unchanged ^{14}C-quazepam appeared in plasma very rapidly with peak plasma levels (10 ng/ml) occurring 0.5 hour after drug administration; subsequently plasma ^{14}C-quazepam declined with an elimination half-life of 1.2 hours. At peak plasma concentration, unchanged drug was less than 3% of total plasma radioactivity, indicating that, in the mouse, quazepam underwent extensive first pass metabolism.

Other major components of plasma radioactivity were Sch 15725 (2-oxoquazepam), Sch 17514 (N-desalkylflurazepam, Sch 23324 (3-hydroxy Sch 15725) and conjugated Sch 23309

(3-hydroxy Sch 17514). Sch 15725 reached a peak level (13 ng/ml) 0.5 hour after drug administration and declined with an elimination half-life of 1.6 hours; Sch 17514 reached a maximum level (219 ng/ml) 1.0 hour after dosing and declined with an elimination half-life of 1.2 hours.

Tissue Distribution

Observations at 1, 5 and 24 hours after a single oral dose of ^{14}C-quazepam (5 mg/kg), showed that the highest concentrations of radioactivity were present in the stomach and intestine. For other tissues, the radioactivity relative to plasma concentrated in the liver (1, 5 and 24 hrs) and to a smaller extent in the kidneys (at 1 and 5 hrs), epididymal fat, heart and lungs (at 5 hours). All other tissues which were examined, contained levels of radioactivity equal to or lower than plasma. Most of the radioactivity was cleared from all tissues within 24 hours, indicating that, in the mouse, quazepam and metabolites were not stored in any tissue.

Excretion

After a single oral dose of ^{14}C-quazepam (5 mg/kg), approximately 98% of the dose was excreted (urine, 37%; feces, 61%) within four days; most of the dose (88%) was eliminated during the first 24 hours.

After a single intravenous dose of ^{14}C-quazepam (5 mg/kg), approximately 100% of the dose was excreted (urine, 43%;

feces, 57%) within four days; most of the dose (87%) was excreted during the first 24 hours.

Metabolism

After both oral and intravenous single doses (5 mg/kg) of ^{14}C-quazepam, the mouse excreted the radioactivity in the urine primarily as Sch 23309 (mostly conjugated) and non-identified polar material. Unchanged ^{14}C-quazepam and other quazepam metabolites were present only in small or trace amounts.

Placental Transfer

Method

To evaluate transplacental passage, single oral doses (5 mg/kg) of ^{14}C-quazepam were given to two groups of 12 pregnant mice each, at the post-embryonic period (day 12 of pregnancy) and near-term (day 18 of pregnancy), respectively.

Tissue Distribution

After 12-day pregnant mice received oral ^{14}C-quazepam, the lowest concentrations of radioactivity were present in the amniotic fluid and fetuses. For all time periods (1, 5 and 24 hours post-dose) the mean level of radioactivity in the fetus was 44% of the level measured in maternal plasma. In maternal tissues, the highest concentrations of radioactivity were present in the G-I tract followed by liver, kidneys, ovaries, lungs and brain. The maternal tissue and fetal radioactivity levels

decreased at approximately the same rate as maternal plasma radioactivity during the 5- to 24-hour post-dose period.

In the 18-day pregnant mice who received oral ^{14}C-quazepam, the tissue distribution pattern of radioactivity was similar to the 12-day pregnant mice. At 18 days, fetuses and maternal plasma had similar levels of radioactivity for each time interval (1, 5 and 24 hours post-dose). Furthermore, fetal and maternal tissues had the same distribution pattern of radioactivity; the levels of radioactivity were highest in liver followed by kidneys, lungs and brain. However, fetal tissues contained considerably less radioactivity than the corresponding maternal tissues. Except for amniotic fluid, all tissues (maternal and fetal) contained significantly lower radioactivity at 24 hours than at 5 hours.

Conclusions from these results indicate that:

1. Quazepam and its metabolites crossed the placental barrier more readily on day 18 of pregnancy than on day 12.
2. Concentration of radioactivity in fetal tissues (day 18) were considerably lower than that in corresponding maternal tissues.
3. The radioactivity did not accumulate in the fetal tissues.
4. The radioactivity in the fetuses and maternal plasma had similar metabolic profiles; however, the fetuses had lower amounts of polar metabolites.

2) RAT[14]

Method

In the rat, preliminary studies on absorption, tissue distribution and excretion were evaluated in 73 male Sprague-Dawley rats (250 to 300 grams) with single doses of ^{3}H-quazepam given orally (5 and 10 mg/kg) and intravenously (1 and 5 mg/kg).

Absorption

^{3}H-quazepam was rapidly and totally absorbed after oral administration as indicated by the plasma levels of radioactivity and excretion data. Maximum plasma radioactivity occurred one hour after 10 mg/kg of oral ^{3}H-quazepam, however, the concentrations of radioactivity were low (210 ng quazepam equiv./ml) and decreased rapidly.

Following intravenous dosing (1 mg/kg) the plasma radioactivity declined rapidly from 240 ng quazepam equiv./ml at 5 minutes to 20 ng quazepam equiv./ml at 4 hours.

Tissue Distribution

The concentrations of radioactivity in various tissues after oral (10 mg/kg) and intravenous dosing (1 mg/kg) were generally low except for liver and intestine; lowest concentrations were present in plasma.

Excretion

Biliary excretion of the radioactivity after oral (10 mg/kg) and intravenous (5 mg/kg) ^{3}H-quazepam was rapid and extensive. Approximately 44% of the oral dose and 66% of the intravenous dose, administered to rats with cannulated bile duct, were recovered in the bile within 5 hours.

The rat excreted most of the radioactivity in the feces following either oral or intravenous dosing. Only 10% of the oral and intravenous dose was excreted in the urine over a 4-day period. The radioactivity eliminated in the feces over the same period was 72% of the intravenous dose (5 mg/kg), and 82% to 83% of the oral dose (5 and 10 mg/kg).

The data indicated that after oral and intravenous ^{3}H-quazepam, the rat eliminated drug-related radioactivity rapidly and primarily through the bile. As a result of the rapid elimination, the plasma levels of radioactivity were very low which may explain the lack of pharmacologic activity in the rat.

3) HAMSTER

Method

The absorption, tissue distribution, metabolism and excretion of quazepam were studied in 72 (twelve groups of 6 animals each) male LVC Syrian hamsters (70 to 95 grams) following single oral (5 mg/kg) and intravenous (1 mg/kg) doses of ^{14}C-quazepam.

Absorption

In hamsters, ^{14}C-quazepam absorption was very rapid and at least 94% complete as indicated by the plasma radioactivity and excretion data after oral and intravenous administration. Mean peak plasma concentration of radioactivity (988 ng quazepam equiv./ml) occurred within 0.5 hour of an oral dose of ^{14}C-quazepam; subsequently the plasma radioactivity declined with an elimination half-life of approximately 35 hours.

In plasma, a very small percentage of radioactivity was unchanged drug. At peak level (28 ng/ml), attained 0.25 hours post-dose, unchanged ^{14}C-quazepam accounted for only 3% of plasma radioactivity, indicating that, in the hamster, the drug underwent extensive first pass metabolism. Following peak level, ^{14}C-quazepam declined with an elimination half-life of 2.4 hours.

Other major components of plasma radioactivity were Sch 15725, Sch 17514, Sch 23309 and conjugated Sch 23324. Sch 15725 peaked (100 ng/ml) at 0.25 hours and declined with an elimination half-life of 1.9 hours; Sch 17514 reached maximum level (84 ng/ml) at 0.5 hour and declined with an elimination half-life of 0.6 hours.

Tissue Distribution

After a single oral dose of ^{14}C-quazepam in the hamster, tissue distribution of radioactivity was evaluated at 1, 5 and 24 hours. High concentrations of radioactivity were present in the

stomach and intestine. For other tissues, the radioactivity relative to plasma concentrated considerably in the liver and to a small extent in the prostate, kidneys, epididymal fat and pituitary. All other tissues investigated contained levels of radioactivity equal to or lower than plasma. For all tissues, the radioactivity was considerably lower at 24 hours than at 1 and 5 hours post-dose. This indicated that ^{14}C-quazepam and its metabolites were not stored in any tissue.

Excretion

Following a single oral dose of ^{14}C-quazepam, approximately 97% of the radioactive dose was excreted (urine, 54%; feces, 43%) over a 7-day period. Similarly, after intravenous administration of ^{14}C-quazepam, approximately 97% of the dose was excreted (urine, 57%; feces, 40%) over a 7-day period.

Metabolism

^{14}C-quazepam was almost totally metabolized in the hamster. Most of the radioactivity excreted in the urine after oral and intravenous dosing was conjugated Sch 23309, conjugated Sch 23324 and non-identified polar material. Unchanged drug and other quazepam metabolites were present only in small or trace amounts.

4) SQUIRREL MONKEY[13]

Method

The absorption, metabolism and excretion of quazepam was investigated in 12 male squirrel monkeys (960 to 1145 grams) following single oral (10 mg/kg) and intravenous (1 mg/kg) doses of ^{14}C-quazepam.

Absorption

In squirrel monkey ^{14}C-quazepam absorption was slow and complete. These conclusions are based upon the plasma levels of radioactivity and excretion patterns after oral and intravenous administration. Mean peak plasma concentration of radioactivity (2161 ng quazepam equiv./ml) occurred 16 hours after oral dosing with ^{14}C-quazepam. Thereafter, the plasma radioactivity declined with an elimination half-life of approximately 43 hours.

Unchanged drug accounted for a very small percentage of total plasma radioactivity. At peak plasma concentration (34 ng/ml), two hours after dosing, unchanged ^{14}C-quazepam represented only 4% of plasma radioactivity, indicating extensive first pass metabolism. Plasma ^{14}C-quazepam declined with an elimination half-life of approximately 10 hours.

Sch 17514 accounted for most of the plasma radioactivity. The plasma concentration of Sch 17514 increased slowly to a peak value of 1416 ng/ml 16 hours after ^{14}C-quazepam oral dosing.

Subsequently Sch 17514 declined with an elimination plasma half-life of approximately 43 hours.

Sch 15725 was also a major component of plasma radioactivity. This compound reached a maximum plasma level (41 ng/ml) two hours after dosing and declined with an elimination half-life of approximately 13 hours.

Following intravenous administration of ^{14}C-quazepam, the plasma radioactivity declined slowly. Unchanged drug, which for the first 15 minutes after dosing represented most of the plasma radioactivity, disappeared from plasma with an elimination half-life of approximately 13 hours.

Excretion

The squirrel monkey excreted the radioactive dose almost totally in the feces. Approximately 79% of the intravenous and 84% of the oral dose were eliminated in the feces over a 7-day period. Only 1% of the dose was excreted in the urine over the 7-day period after either intravenous or oral dosing.

Metabolism

Due to minimal amounts of radioactivity in the urine, the metabolic profile of ^{14}C-quazepam in the squirrel monkey was investigated in the feces following oral and intravenous dosing. Sch 23324 (mostly non-conjugated) was the major metabolite of quazepam in the feces; unchanged drug and other metabolites were present in small amounts.

5) Special Studies:

Liver Drug Metabolizing Enzyme Systems

The effect of quazepam on liver drug metabolizing enzyme systems was evaluated in 24 mice and 4 hamsters after they received high oral doses (100 mg/kg/day) for seven consecutive days. Comparisons were made to a positive control (sodium phenobarbital) and the drug vehicle.

Measurements were made on liver weight, liver to body weight ratio, hepatic microsomal protein, hepatic cytochrome P-450, and the in vitro activities of aniline hydroxylase and benzphetamine N-demethylase.

In mice, quazepam slightly increased liver weight (7%), liver to body weight ratio (9%), and hepatic cytochrome P-450 (47%); quazepam had no effect on the activity of either aniline hydroxylase or benzphetamine N-demethylase.

In hamsters, a considerable increase in hepatic cytochrome P-450 (115%) occurred with quazepam. Although the increase in hepatic microsomal protein was only 22%, and benzphetamine N-demethylation was 32%; aniline hydroxylation was not affected.

ACUTE TOXICITY

Species	Strain	Sex	Age	Route	LD 50
Mouse	CF-1	M		p.o.	5000
Mouse	CF-1	F		p.o.	5000
Mouse	CF-1	M		i.p.	781-928
Mouse	CF-1	F		i.p.	794-1025
Rat	Charles River D	M		p.o.	5000
Rat	Charles River D	F		p.o.	5000
Rat	Charles River D	M		i.p.	3072
Rat	Charles River D	F		i.p.	2749

Observed Effects:

Oral dosage

Mice showed signs of hypoactivity, deep respiration, ptosis, head shaking, ataxia, and straub tail. In the rat, doses of 5000 mg/kg produced no clinical signs.

i.p. dosage

Mice again showed hypoactivity, deep respiration, ptosis, head shaking, ataxia, and straub tail.

Rats given quazepam i.p. showed the following signs near death: prostration, ptosis, slow respiration, oligodipsis, anorexia, hypoactivity, passivity, sluggishness, ataxia, piloerection, and chromodacryorrhea.

Beagle dogs receiving 1000 mg/kg p.o. showed excitement and salivation. During the excitement stage there was a rise in body temperature, heart rate and respiration rate.

Table II. - ACUTE TOXICITY OF BENZODIAZEPINES IN MICE

Route	QUAZEPAM	TEMAZEPAM	OXAZEPAM	CHLORDIAZEPOXIDE	DIAZEPAM	LORAZEPAM	CLONAZAM
Oral	>5000[a]	800-1900	>5900	794(735-857)	1901(1632-2214)	>5000	6881(504-918)[a]
	>5000[b]						820(686-980)[b]
I.P.	845(781-528)[a]	909-1700	>5000	401(341-473)	774(732-819)	873.6	510(442-506)[a]
	921(794-1025)[b]						615(515-708)[b]

LD_{50} mg/kg (fiducial limits p = 0.95)

[a] - male
[b] - female

Table III. - ACUTE TOXICITY OF BENZODIAZEPINES IN RATS

ROUTE	QUAZEPAM	TEMAZEPAM	OXAZEPAM	CHLORDIAZEPOXIDE	DIAZEPAM	LORAZEPAM	CLOBAZAM
Oral	>5000[a]	2000-8000	>5000	537(472-611)	1517(1237-1862)	>5010	6000(4880-7380)
	>5000[b]						
I.P.	3072(2569-3635)[a]	600	>5000	276(247-309)	661(542-805)	805(753-861)	740-1526
	2749[b]						

LD_{50} mg/kg (fiducial limits p = 0.95)

[a] - male
[b] - female

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CHRONIC TOXICITY STUDIES

One-Year Toxicity in Hamster

Animal: LVG Syrian hamsters

Dose: 0, 3, 20, 120 mg/kg daily in diet

No. and Sex per group: 36M, 36F (72M, 72F in control)

Interim Sacrifice: none, except for moribund

Duration: 51 weeks

The doses used in this study ranged from 5 to 200 times the maximum proposed human dose of 0.6 mg/kg. For comparison, one group of hamsters was treated with diazepam at 120 mg/kg/day.

Observed Effects:

The sponsor used the hamster for long-term toxicity because the drug is rapidly metabolized in the rat and the toxicity profile of quazepam in hamsters is similar to that of 1,4 benzodiazepines in other rodent species. Dose-related ataxia was observed in males and females given quazepam as well as in the hamsters given diazepam. Incidence and degree of ataxia was similar at 120 mg/kg for both diazepam and quazepam treated hamsters. Both drugs caused alopecia after three to six months. Tremors, teeth chattering, and increased activity were noted at all doses of quazepam and in diazepam-treated hamsters. There was no other condition observed that was thought to be drug related.

Doses selected for the study were based on the results of a 30-day pilot toxicity study where it was found that liver weights were increased at the 125 mg/kg level and transaminase values were increased at the 250 mg/kg level.

animals dying or killed in moribund condition

Mortality

Quazepam dose (mg/kg)	0	3	20	120	120 diazepam
males	23/72	19/36	9/36	14/26	9/36
females	53/72	21/36	21/36	25/36	16/36

Microscopic examination showed that the hamsters in all groups generally died from enteritis, atrial strombosis and heart failure, or renal amyloidosis and uremia. These diseases were considered sponsaneous and unrelated to dosing.

Body weight/food consumption/water consumption

Body weight gains were higher than controls in HD and diazepam groups, amounting to an increase of 5-9 grams in group mean body weights for those groups. Only males were affected. During the post-dose washout period, lost body weight was recovered. Males in all dosage groups showed slightly higher food consumption than controls.

Hematology and blood chemistry

No compound-related changes were observed in the hematology values. The group mean cholesterol values were statistically significantly less than controls in the MD group, HD group and diazepam group (females only) at weeks 13 and 25. Group mean albumin/globulin ratios in HD and diazepam treated hamsters were slightly greater than control values. The significance of these findings is unclear at this point.

Urinalysis

The 24-hour urine volumes of treated females tended to be higher than control values. There was a corresponding increase in water intake by these hamsters, which also tended to produce urine with below normal osmolality or specific gravity. The changes were not related to dose and are considered to be of little biological significance since the changes were small and disappeared over time.

Ophthalmic examination:

Eyes of all hamsters were examined once during the acclimation period. All hamsters (except those bled for clinical pathology measurements or compound plasma determination) were also examined during weeks 24 and 51 of the dosing period and at post dose week 5. In each case, eyes were examined with a Fison indirect ophthalmoscope. No ocular changes were found in any of the hamsters, except for physical injury caused by an orbital sinus bleeding procedure.

Organ Weights

Group	Organ showing small mean relative weight change
high dose males	+liver, +kidney, +adrenal
high dose females	-kidney, -adrenal
mid dose females	-adrenals, -ovaries
diazepam males	+liver, -seminal vesicles
diazepam females	-adrenal, -kidney

Obviously, no conclusion can be drawn from the sporadic occurrences.

Gross Pathology

No compound-treated changes were seen at necropsy in any of the hamsters in this study. Alopecia was observed in all groups with a slightly higher incidence in the treated groups. Gross lesions observed were either spontaneous or caused during sacrifice.

Histopathology

In HD hamsters, bile retention in the liver occurred in 22/27 males and and 7/30 females necropsied during the study or at the scheduled necropsy. Benzodiazepine-induced bile stasis has been reported in other species. Hepatocellular hypertrophy in treated hamsters was seen in 4/25 MD males, 2/27 HD males, and 2/36 HD females. In hamsters which were sacrificed during the postdose observation period, hepatocellular hypertrophy occurred in 2/11 MD males and 1/9 HD males. Bile retention was observed in the liver of 1/24 diazepam males during study and 4/12 diazepam males sacrificed in the post dose period. Hepatocellular hypertrophy occurred at 1/24 in the males getting diazepam (during study) and at a frequency of 1/12 in the group killed after the post dose period. Many hamsters showed signs of salmonellosis and phlebothrombosis and this was considered to be incidental to treatment. Other spontaneous diseases included enteritis, atrial thrombosis and heart failure, and renal amyloidosis and uremia.

Since most observed toxic effects of quazepam occurred at the 120 mg/kg dose level (200 x the maximum proposed human dose) it would be safe to assume that a maximally tolerated dose for quazepam would lie at somewhat less than 120 mg/kg, but greater than 20 mg/kg daily.

HAMSTER CHRONIC TOXICITY

Summary and Evaluation

The number of animals used, duration of the study, and dosage range employed were acceptable for this type of long term toxicity in the rodent. The dose range employed was sufficient both to demonstrate evidence of toxicity as well as allow for acceptable long term survival of the animals. Diazepam was given as a comparative control in a dose sufficient to cause toxic signs. Mortality among the hamsters was equally divided between dosed and control groups, and was attributed to enteritis, atrial thrombosis, and heart failure, or renal amyloidosis and uremia. These conditions were regarded as spontaneous and not drug related. Both diazepam and quazepam elicited ataxia, alopecia, tremors, and hyperactivity at the 120 mg/kg level. While neither drug altered water consumption, both drugs were associated with enhanced body weight and food consumption in the males at the 120 mg/kg dose. Only those females receiving diazepam experienced an increase in food consumption. The drugs did not alter hematology or clinical chemistry values, and drug related gross physical changes were not seen at necropsy. Histopathology revealed only bile retention as a significant finding and only at the high dose level (120 mg/kg). Bile stasis is known to be produced by other benzodiazepines in other species as well.

One Year Monkey Toxicity

Animal: squirrel monkey (Solmiri sciureus)

Dose: 0, 2, 10, 50 mg/kg P.O. by gavage

No. and Sex per Group: 5M, 5F

Duration: 52 weeks (no interim sacrifice)

Doses used were up to 83 times the proposed maximum human dose of 0.6 mg/kg/day. One group of monkeys, for comparison, was treated with 50 mg/kg diazepam (about 63 times the 40 mg/day therapeutic dose for man). Two monkeys from each group were observed during a 4-week post dose period.

Mortality

1 control female, 1 LD male. Deteriorating health preceded death. During the 4 week post-dose period 1 LD male, 1 MD male, and all 4 diazepam treated monkeys died or were sacrificed in poor condition. Their body weights had decreased considerably and the animals had shown repeated bouts of convulsions. Pale livers, kidneys, and fatty degeneration of the liver were noted.

Gross Observations

Dose and drug-related sedation, somnolence, ataxia, and tremors were observed in monkeys taking either drug. Frequency and degree was greatest during first three weeks of study. During the first week of study, several HD and diazepam treated monkeys were unable to move without falling. There were also incidental findings of alopecia, lacrimation, emesis, foot and tail sores and ulcers, tooth absesses, salivation, and distended abdomen.

Ophthalmoscopic Examination

These tests using a Fison indirect ophthalmoscope, before the start of the study and again at weeks 24 and 48 of the dosing period and at post dose week 4 did not reveal any ocular changes attributable to dosing witheither quazepam or diazepam.

Evidence of Possible Addiction Liability

During the 4 week post dose period, the clinical signs were similar for the monkeys in the diazepam and quazepam groups; ataxia, emesis, tremors, or convulsions were observed within 3 days after cessation of dosing. The convulsions usually lasted for only a few minutes and were followed by either complete recovery or death. One monkey found convulsing, prostrate, and near death on the eigth day of the post dose period was redosed with a single dose of diazepam. This monkey showed signs of recovery in 20 minutes and appeared relatively healthy for about 3 days when it again convulsed. The monkey was found dead about 9 days after being redosed with diazepam.

Body Weight and Food Consumption

Group mean values for body weight and food consumption did not differ appeciably among the groups.

Other Effects

On day 1, a dose-related decrease occurred in mean values for body temperature, heart rate, and respiration rate. Thereafter, mean values for these parameters did not differ significantly from control values. Few drug related changes were revealed in the clinical laboratory determinations. High alkaline phosphatase levels (330 IU/L) were found in HD females only. Compound-related increases in SGPT values were observed in 3 HD males and 4 HD females. The values were elevated (851U/L) in males at weeks 2, 13, 26, 452, and in females at weeks 13 and 52. Slight elevations in SGOT values were observed also in 2 females at week 13 and in 3 males at weeks 2 and 13. No compound-related changes were seen in urine chemistry values.

Gross Pathology

Organ Weights		Individual Organ Weights (mg)		
Dose mg/kg	# animals	Tests	Prostate	Seminal Vesicles
0	3	3.76	0.73	1.71
		3.05	0.32	0.89
		4.22	0.77	2.57
diazepam 50	3	3.73	0.35	0.68
		0.62	0.04	0.12
		1.58	0.18	0.33
2	2	2.72	0.42	1.15
		3.40	0.78	1.80
10	3	3.99	0.75	1.56
		2.23	0.48	0.80
		2.01	0.39	0.93
50	3	3.08	0.27	0.56
		2.44	0.35	0.85
		2.92	0.14	0.69

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Ratios Organ Weight/Body Weight (Males)

Dose mg/kg	# of Animals	Testes	Prostate	Seminal Vesicles	Liver
0	3	0.357	0.069	0.161	1.509
		0.355	0.037	0.103	1.666
		0.391	0.971	0.238	1.602
diazepam 50	3	0.397	0.037	0.072	2.181
		0.089	0.006	0.017	2.343
		0.247	0.028	0.052	2.703
2	2	0.247	0.038	0.105	1.645
		0.340	0.078	0.180	1.450
10	3	0.403	0.076	0.158	1.687
		0.259	0.056	0.093	1.779
		0.251	0.049	0.116	1.700
50	3	0.376	0.033	0.068	2.037
		0.284	0.041	0.099	1.930
		0.332	0.016	0.078	2.034

Ratios Organ Weight/Body Weight (Females)

Dose mg/kg	# Animals	Liver
0	2	2.049
		2.316
diazepam 50	3	3.000
		2.896
		2.808
2	3	1.855
		1.712
		1.869
10	3	2.238
		2.403
		2.517
50	3	2.055
		2.167
		1.809

At the end of the 52 week study, the absolute and relative weights of the testes and prostate and seminal vesicles were below control valvues in HD males. In the diazepam group the sama holds true (see tables above). The relative weights of the testes were below control values in 2 LD and 2 MD monkeys. The absolute weights of the testes were below the control values in LD and MD monkeys. The relative liver weights were higher than control values for both males and females at the HD quazepam level and in the diazepam group.

Except for decreased size of the genitals in one diazepam treated male, no compound related lesions were reported on gross examination.

Microscopic examination showed small foci of necrosis in the livers of 2 HD females and 1 HD male. Fatty change in the liver was moderate in 1 MD and 1 HD male and severe in 1 LD female. The fatty change was attributed to mobilization of body fat and its deposition in the liver secondary to poor health of the monkeys. The decreased testicular weights observed in some monkeys could not be accounted for by microscopic findings except for atrophic gonadal adnexa observed in 2 MD males. Diazepam treated monkeys showed atrophy of gonadal adnexa in 2 of the 3 monkeys examined.

Incidental findings included lung lesions (interstitial pneumonia, atalectasis and lymphomonocytic infiltrates) and intestinal inflammation secondary to parasitic infection. One LD female had an adrenal adenoma and a thyroid adenoma.

MONKEY CHRONIC TOXICITY

Summary and Evaluation

Squirrel monkeys were chosen for the test to fulfill the requirement for a nonrodent test model after preliminary experiments showed quazepam to be pharmacologically active in this species. The dose of drug selected for the test were based on the results of a pilot 13 week study. In that study a dose of 50 mg/kg was well tolerated, but during a post dose recovery period, signs of withdrawal occurred including hyperactivity convulsions, and decreased food consumption. For the one year study, doses of 2, 10, and 50 mg/kg were employed as was a 50 mg/kg diazepam treated group. The quazepam doses were 3, 17 and 83 times for proposed human dose of 0.6 mg/kg maximum. The number of animals employed was adequate at 5 M and 5 F per dose group. Three monkeys of each sex groups were killed and examined at the end of 52 weeks. The remaining 2 of each groups were killed after a 4 week post-test washout period. All monkeys survived the 52 week test period except for 1 control and one quazepam treated low dose monkey. Of the monkeys retained for the 4 week post dose followup, several in both diazepam and quazepam groups died or were killed in moribund condition. Weight loss and convulsions were observed in these animals, probably a reaction to withdrawal of the drug. The principal behavior changes during the test were sedation, somnolence, ataxia, and tremor. These occurred with both diazepam and quazepam. Hematology, blood chemistry, and urine chemistry determination revealed no meaningful compound related effects. Sporadic adverse findings at necropsy did not appear drug related and were generally attributed to the poor condition of several monkeys at the end of the testing period.

Reproduction and Teratology Studies

NCA 18-708

Fertility and General Reproductive Performance of the Mouse - Segment I

Animal: Charles River CD-1 mouse

Dosage: 0, 6, 18, 54 mg/kg daily by intubation; positive control with 54 mg/kg diazepam

per group: 15 males, 30 females

Treatment

Males at least 6 weeks old were treated for 8 weeks prior to mating to test for effects of drug on spermatogenesis. Females, sexually mature, were treated for 2 weeks prior to mating the through mating, gestation, and lactation. Dosing continued until sacrifice of the F0 generation after selection of F1 animals. In each group, 14 females were killed on day 17 of gestation to see effects of drug on in utero development, while 15 or 16 females in each group were allowed to rear litters to 21 days postpartum to assess drug effect on parturition, lactation, and post-natal development and behavior of offspring.

Observed Effects and Mortalities

In all test groups treatment with quazepam was associated with dose-related sedation. Degree of sedation was similar in HD and diazepam groups. One control female died and one male and female from each of HD and diazepam groups were killed due to deterioration of condition. Body weights and food consumption were relatively unaffected.

	Dose mg/kg				
Mating performance: Males	0	6	18	54	diazepam 54
# Males successfully impregnating 2 females:	15/15	15/15	10/15	8/15	10/15
Impregnating 1 of 2 females	0/15	0/15	4/15	5/15	5/15

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Mating performance: Females	Dose mg/kg 0	6	18	54	diazepam 54
# Females paired	30	30	30	30	29
# did not mate	2	3	5	5	5
pregnancy rate %	100	100	80	70	83
Data from 16 dams allowed to litter:					
# live young	11.9	11.3	9.6	10.8	11.4
# embryonic deaths	0.9	1.2	1.4	2.3	1.2
implantations	12.7	12.7	11.0	13.0	12.6
% post-implantation loss	6.7	10.1	13.0	17.0	9.9
% pup loss by day 21 pp	11	24	28	79	80

A reduced number of pregnancies was found at MD, HD, and diazepam. The lower pregnancy rate was associated with reduced numbers of dams showing clear evidence of mat ng. Duration of gestation was essentially comparable for all groups. The table above shows a correlation between increasing dose and decreased pregnancy rate, increased embryonic death, increased post-implantation loss and increased total pup loss. There was no evidence of unusual fetal abnormalities. It is apparent that quazepam interferes with reproductive performance in the mouse when given at doses of over 60x the proposed human dose.

F1 generation:

It was hard to assess the effect of quazepam on the generation because of the severe loss of pups in the MD and HD groups. Data available for LD and MD groups show some retarded development at MD, little or no effect at LD.

Results from most of the tests in this study suggest that the 54 mg/kg dose of quazepam produces qualitative and quantitative results similar to those seen with 54 mg/kg diazepam.

Teratology Studies in Mouse and Rabbit

A. MOUSE TERATOLOGY

per group: 25

Species: Charles River CD-1 strain mice

Dose: 0, 3, 20, 120 mg/kg/day from day 6-15 after mating, killed on day 18

Positive control: diazepam 160 mg/kg/day

Doses of quazepam used were about 5, 33, and 200x the clinical dosage. Diazepam was used also at about 200x the clinical dosage. The study is to determine the affects of the drug on fetal development. Drug was given by esophageal intubation.

Maternal Findings

All mice in HD group were hypoactive from within a half hour up to 3 hours after being dosed. Same for diazepam group. Two mice died from aspirating the drug suspension. Dams that survived to the end of the study showed no unusual clinical signs at time of sacrifice. The percentage of mice in each treated group and diazepam group that became pregnant was not significantly different from that in control (see table). There was also no real difference between treated and control in mean number of implantations, resorptions, and the percentage of dams/group that had resorptions. HD and diazepam treated dams ate more and gained weight by the end of the stuay (day 15) but lost the weight during the 3 day post-dosing period.

Offspring

Litter size, fetal distribution in utero, sex distribution, and fetal body weights were comparable between treated and controls.

Seven of the 1036 pups examined had major malformations, one in a quazepam-treated mouse and 6 in diazepam treated mice. There was some minor skeletal variations observed such as extra ribs and fused ribs. Retarded ossificaton of sternabrae, vertebrae, distal phalanges and suproccipital bones was greater in the fetuses of MD, HD and diazepam mice when compared with control, but still within the "normal" range according to literature reports. This is a common mouse variant and has been

reported to range in incidence fro 2-93% in this strain of mouse. The sponsor speculates that reduced food consumption in the dams in these treatment groups may be a contributing factor in the incidence of retarded ossification observed.

Essentially quazepam does not appear to be a teratogen in the mouse although high doses (200x human dose) of quazepam as well as diazepam may slow the process of bone ossification.

STUDY NO. 78009
SCH 16134 IN MICE - SEGMENT II

Mouse Segment II

TABLE 2. Summary of Reproduction Data

	Control	SCH 16134 3.0mg/kg[a]	SCH 16134 30mg/kg	SCH 16134 120mg/kg[a]	Positive Control[1]	P-value
Total Mated	25	23	25	25	25	
No. Pregnant	19	17	19	21	22	
% Pregnant	76	68	76	84	88	p>.10
No. Remaining Preg. to Day 18	19	17	19	21	21	
No. That Died Before Day 18	0	0	0	1	1	
Total No. of Implantations	228	183	218	234	247	
Mean ± S.E.	11.8 ± 0.3	11.4 ± 0.4	11.5 ± 0.3	11.7 ± 0.5	11.8 ± 0.5	p>.10
Total No. of Resorptions	14	18	27	19	18	
Mean ± S.E.	0.7 ± 0.2	1.0 ± 0.3	1.4 ± 0.3	1.0 ± 0.2	0.9 ± 0.2	p>.10
No. of Females Resorbing	8	10	13	12	13	
%	42	43	68	48	87	p>.10
No. of Litters	19	16	19	20	21	
No. of Live Offspring	200	166	190	215	229	
No. of Dead Offspring	3	1	1	0	0	
Mean Litter Size No. ± S.E.	11.1 ± 0.3	10.4 ± 0.3	10.1 ± 0.5	10.8 ± 0.4	10.9 ± 0.5	p>.10

[a] Per Dr. Klein, mouse #42 in the 3 mg/kg group and mouse #88 in the 120 mg/kg group delivered prior to sacrifice on Day 18 and are excluded from the statistical analyses on implantations, number of litters, litter size, sex distribution, and body weights of offspring. Mouse #123 in the positive control group died and resorbed all conceptuses and is included only in pregnancy rate analysis.

[1] SCH 9584 (Diazepam, 160 mg/kg).

STUDY NO. 79009
SCH 16134 IN MICE - SEGMENT II

Mouse Segment II

TABLE 2 (cont.). Summary of Reproduction Data

	Control	SCH 16134 3.0mg/kg	SCH 16134 20mg/kg	SCH 16134 120mg/kg	Positive Control[1]	P-value
Distribution of Offspring In Uterus						
No. in Left Horn	102	75	96	103	117	
No. in Right Horn	109	92	95	112	112	
% in Left Horn	48	45	50	48	51	p>.10
Distribution of Males and Females						
No. of Males	114	88	98	114	120	
No. of Females	97	79	93	101	109	
% Males	54	53	51	53	52	p>.10

[1] SCH 9584 (Diazepam), 160 mg/kg.

TABLE 3. Findings of Soft Tissue and Skeletal Examination

	Vehicle Control	SCH 16134 3.0 mg/kg	SCH 16134 20.0 mg/kg	SCH 16134 120.0 mg/kg	Positive Control (Diazepam) 160.0 mg/kg
Number Delivered	208 (212)	166 (178)	190 (191)	215 (225)	229 (230)
No. Examined For:					
a) Soft Tissue Defects	62 (64)	51 (55)	60 (61)	70 (73)	75
b) Skeletal Defects	146 (148)	115 (123)	130	145 (152)	154 (155)
Major Malformations					
No. With Cleft Palate	0	1	0	0	3
No. With Exencephaly	0	0	0	0	1*
No. With Open Eyelids	0	0	0	0	2 (3)
Total No. With Major Malformations	0	1	0	0	5 (6)
Minor Developmental Variations					
No. With Dilated Renal Pelves	0	0	0	1	2
Extra Cervical Ribs					
a) Single	2 (2)	6 (9)	8	7	7
b) Pair	5 (5)	2 (3)	5	8	1
Extra Thoracic Ribs					
a) Single	18 (18)	5	16	24	16
b) Pair	30 (31)	18 (19)	23	32	21
Unossified Distal Phalanges	0	1	1	2 (6)	9 (10)

Note: Those values in parentheses also include the findings from late resorptions, dead pups, and offspring delivered early.

* This pup also had open eyelids.

TABLE 3 (cont.). Findings of Soft Tissue and Skeletal Examination

	Vehicle Control	SCH 16134 3.0 mg/kg	SCH 16134 20.0 mg/kg	SCH 16134 120.0 mg/kg	Positive Control (Diazepam) 160.0 mg/kg
Sternebrae					
a) Unossified	0	0	2	1 (2)	8
b) Bipartite	4 (5)	2	9	11 (12)	5
c) Reduced Ossification	0	0	1	0 (0)	4
d) Assym-metrical	0	2	1	0 (0)	1
Unossified Caudal Vertebrae	0	0	0	1 (2)	0 (1)
Reduced Ossif. of Ischium and Pubis	0	0	0	1	0
Cervical Vertebrae					
a) Unossified	0	0	0	0 (1)	0
b) Unossified Centra	0	0	0	1 (3)	2
c) Hemicentra	1	0	0	0	0
Supraoccipitals					
a) Bipartite	0	0	6	3 (4)	8
b) Reduced Ossification	1	0	1	1	0 (1)
c) Assym-metrical	1	0	0	0	1
Fused Ribs	1	1	0	0	0
Total # With Minor Variations	63 (64)	37 (42)	73	92 (103)	83 (86)
% With Minor Variations	30	22 (24)	38	43 (46)	36 (37)

Note: The incidences of retarded ossification (based on no. examined for skeletal defects) in the vehicle control, 3 mg/kg, 20 mg/kg, 120 mg/kg and in the positive control groups were 5%, 5%, 16%, 13% and 25%, respectively.

B. RABBIT TERATOLOGY

Species: New Zealand White Rabbits (average weight = 3.8 kg)

per group: 14 treated, 16 control

Dose: 0, 10, 20, 40 mg/kg daily by intubation from day 6-18 after mating, killed on day 30 after mating. No diazepam control was used.

Maternal Findings

Some animals from each treatment group as well as controls developed sicknesses that included anorexia, congested lungs, pyrometra, snuffles, ruptured stomach -- none of which occurrences could be correlated with drug administration.

Incidence: 4 control, 4 LD, 3 MD, 5 HD

Other Findings (maternal):	0	LD	MD	HD
Pregnancy rate (%)	81	86	93	85
Implantation	101	113	113	111
Resorptions	20	15	11	21

Offspring	0	LD	MD	HD
Litter size	81	96	92	81
Mean litter size	7.4	9.6	7.7	8.1
Percent males	52	55	46	46
Body Weight	52	46	47	41
24 hr. survival (%)	94	100	100	96

The above tables show a lack of variation in the measured parameters between control and treated rabbits and offspring.

The incidence of minor variations in development in each of the treatment groups was not significantly different from that in controls. The variations consisted of extra ribs and to a lesser extent of retarded ossification of the sternabrae. Only 2 of the 350 pups produced in the study were "abnormal." One MD pup was missing a tail and one HD pup hac an umbilical hernia. The data in this study support the sponsor's view that quazepam is not teratogenic in the rabbit.

NDA 18-708

Segment III Reproduction Study in Mice
(Peri and Post natal)
First of 2 identical studies

Animal: albino mice (Charles River CD-1)

per group: 25F

Dosage group: 0, 3, 9, 18 mg/kg from day 13 after mating to day 21 post-partum diazepam 18 mg/kg was positive control

The mice were allowed to deliver naturally and to rear their offspring to day 21 after parturition at which time dame and offspring were sacrificed. Dose of quazepam were 5, 15, and 30x the proposed maximum human clinical dose of 0.6 mg/kg daily. Diazepam dose used was about 23x its clinical dose of 0.8 mg/kg.

Transient hypoactivity occurred in MD and HD as well as diazepam control mice. Eight mice died, mostly because of lung congestion. Twenty-four mice were killed before end of study because their litters had died. Two of those were control and the others were almost equally distributed among the treated groups.

Length of gestation, labor, litter size, and sex distribution of offspring were not affected by either drug. Mean body weights of offspring in MD, HD and diazepam groups were less than that of vehicle controls on day 4 after birth but by day 21 their body weightrs were comparable to vehicle controls.

Offspring deaths during lactation were increased in all treated groups, mostly occurring between birth and day 4 after birth and attributed to maternal neglect due to drug effect.

Renal changes in the form of hydronephrosis and dilated renal pelves were seen in the offspring of all groups.

Renal Changes

Dose mg/kg	Incidence %
0	0.8
3	2.9
9	4.8
18	9.2
diazepam 18	2.8

This study was repeated to determine if the above renal findings were accepted. The following tables contain a summary of the reproduction data in this study.

Table 2. Summary of Reproduction Data

	SCH 16134					
	Control	1 mg/kg	3 mg/kg	10 mg/kg	Diazepam (10 mg/kg)	Overall P-values (NS = p>.10)
Gestation Length (from Day 0)						
Mean (Days) ± S.E.M.	19.0 ± 0.05 (N=21)	19.1 ± 0.10 (N=22)	19.1 ± 0.06 (N=22)	19.2 ± 0.13 (N=23)	19.0 ± 0.00 (N=22)	NS
Total No. of Implantations	268	280	285	[illegible]	281	
Mean ± S.E.M.	[illegible] (N=21)	[illegible] (N=22)	[illegible] (N=22)	[illegible] (N=23)	12.8 ± 0.40 (N=22)	NS
Total No. Born	254	245	252	261	246	
Mean/Litter ± S.E.M.	12.1 ± 0.31 (N=21)	11.1 ± 0.51 (N=22)	11.5 ± 0.47 (N=22)	11.4 ± 0.45 (N=23)	11.2 ± 0.38 (N=22)	NS
Offspring Deaths[1]						
Day 0 (Birth)						
No. Born	229	198	240	251	246	
No. Dead	4	4	9	12	12	
% Dead	1.7%	2.0%	3.8%	4.8%	4.9%	NS
Days 1-4						
No. Born Alive	225	194	231	239	234	
No. Dead	3	31	62	60	56	
% Dead	1.3%	*** 16.0%	*** 26.8%	*** 25.1%	*** 23.9%	p<.01
Days 5-21						
No. Alive Day 4	222	163	169	179	178	
No. Dead	39	27	42	44	27	
% Dead	17.6%	16.6%	24.9%	24.6%	15.2%	NS
Days 0-21						
No. Born	229	198	240	251	246	
No. Dead	46	62	113	116	95	
% Dead	20.1%	** 31.3%	*** 47.1%	*** 46.2%	*** 38.6%	p<.01

** Significantly different from control, p<.05.

*** Significantly different from control, p<.01.

1 [illegible] the number of dams in each dose group at the postnatal period were not to be included in these analyses since the deaths

Table 2. Summary of Reproduction Data (cont'd)

	HCH 161 µA					
	Control	1 mg/kg	2 mg/kg	10 mg/kg	Diazepam (10 mg/kg)	Overall F-value (NS = p>.10)
Sex Distribution						
Day 0						
No. Males	125	106	130	136	115	
No. Females	102	92	109	114	131	
% Males	55%	53%	54%	54%	47%	NS
Day 21						
No. Males	102	76	71	79	73	
No. Females	81	60	56	56	78	
% Males	56%	56%	56%	58%	48%	NS

NDA 18-708

Repeat of Mouse Segment III Study
(Second of 2 studies)

Animal: Mouse (Charles River CD-1)

per group: 25F

Dosage groups: 0, 9, 18 mg/kg p.o. from day 13 after mating to day 21 post partum diazepam 18 mg/kg was positive control.

Doses used were 15 and 30x proposed human doses. Diazepam control dose was 23x human dose.

Transient hypoactivity occurred in all treated mice. Length of gestation, labor, litter size, sex distribution of offspring and incidence of offspring mortality were not affected by either of the drugs. Mean body weights of offspring in the HD and diazepam groups were reduced compared to control. Of the 284 pups sacrificed on day of birth only one had a defect (dilated renal pelvis) and was from the vehicle control group. None of the pups examined which survived to day 21 or any of those that died during lactation showed hydronephrosis or dilated renal pelves. These findings are in contrast to the previous segment III mouse study using the same techniques and protocol. It is also surprising that the incidence of pup death that was observed previously and attributed to ~~maternal~~ neglect due to drug effect was not seen in the present study.
maternal

TABLE 2: Summary of Reproduction Data

	SCH 16134				
	Control	2 mg/kg	10 mg/kg	Diazepam (10 mg/kg)	Overall P-values (NS = p>.10)
Gestation Length (from Day 0)					
Mean (Days) ± S.E.M.	18.9 ± 0.09 (n = 25)	19.0 ± 0.14 (n = 19)	18.8 ± 0.09 (n = 21)	18.7 ± 0.10 (n = 22)	NS
Total No. of Implantations					
Mean ± S.E.M.	12.0 ± 0.38 (n = 25)	12.0 ± 0.51 (n = 19)	12.5 ± 0.34 (n = 21)	12.5 ± 0.53 (n = 22)	NS
Total No. Born					
Mean/Litter ± S.E.M.	10.7 ± 0.48 (n = 25)	11.0 ± 0.49 (n = 19)	11.1 ± 0.37 (n = 21)	11.1 ± 0.49 (n = 22)	NS
Offspring Deaths[1]					
Days 0 (Birth)					
No. Born	268	248	263	233	
No. Dead	9	8	3	1	
% Dead	3.3%	3.4%	1.2%	0.6%	p>.10 for all comparisons
Days 1-4					
No. Born Alive	181	240	261	170	
No. Dead	10	6	17	19	
% Dead	5.5%	4.3%	10.6%	11.2%	p>.10 for all comparisons
Days 5-21					
No. Alive Day 4	171	234	244	151	
No. Dead	28	22	12	24	
% Dead	16.4%	9.0%	8.3%	15.9%	p>.10 for all comparisons
Days 0-21					
No. Born	268	248	263	233	
No. Dead	45	26	31	44	
% Dead	23.9%	17.6%	19.0%	25.3%	p>.10 for all comparisons

[1] About one-third of the offspring from each litter was sacrificed on the day of birth for soft tissue examination; these offspring were excluded from these analyses.

TABLE 2: Summary of Reproduction Data (Continued)

	BCH 161A				
	Control	2 mg/kg	10 mg/kg	Pleropon (10 mg/kg)	Overall F-value (NS = p>.10)
Sex Distribution					
Day 0					
No. Males	121	99	120	122	
No. Females	140	110	112	123	
% Males	47%	47%	52%	50%	NS
Day 21[1]					
No. Males	65	51	66	58	
No. Females	78	65	66	69	
% Males	45%	44%	50%	46%	NS

[1] It should be noted that about one-third of the offspring from each litter were sacrificed on day 0; therefore the day 0 analysis includes these offspring but the day 21 analysis excludes them.

CARCINOGENICITY STUDIES

Statistical Analysis of Data From Carcinogenicity Studies

Incidence of lesions were analyzed using Fisher's Exact Test. Test data were subjected to a statistical evaluation of variance with the F-MAX test. When differences between groups variances were not significant ($P > 0.01$) a one-way analysis of variance (ANOVA) was performed. If significant differences ($P \simeq 0.10$) among the means were indicated by the ANOVA, Dunnett's test was used to determine which means were different from the controls. When the difference between group variances were significant ($P \leq 0.01$) by the F-MAX test, the mean values between each pair of groups were compared using the Behren-Fisher t-Test. Dunnett's test and the Behren-Fisher t-test were conducted at the 0.05 and 0.01 two-sided risk levels.

QUAZEPAM CARCINOGENICITY STUDY IN HAMSTERS - 18 MONTHS

672 hamsters were randomly divided into 4 dose groups of 56 males and 56 females each and into a control group of 112 males and 112 females. Doses were 0, 3, 20, and 120 mg/kg/day for quazepam and 120 mg/kg/day for diazepam.

The doses selected were based on the results of a one-month pilot study which used doses up to 250 mg/kg/day. Elevated transaminase and liver weights at the 250 mg level were apparently part for the reason for limiting the high dose in this 18 month study to 120 mg/kg/day. The dose levels in this 18 month study were approxiamtely 5, 39, and 200 times the proposed maixmum human dose of 0.6 mg/kg/day. The drugs were administered by food admixture. Measurement of plasma levels of a major metabolite of quazepam indicated that the drug was absorbed at all doses.

The control, diazepam, LD and MD treated males survived 18 months of dosing (11 to 36 survivors per group); 120 mg/kg (HD) males were killed after 73 weeks of dosing (13 survivors) and all groups of surviving females were killed after 57 weeks of dosing at which time 14 to 26 hamsters remained in each group. Of the initial number of hamsters in each group, 50% survived for as long as 55 to 66 weeks for males and 46 to 55 weeks for females. Most of the interim deaths occurred after 30 weeks of dosing and were associated with enteritis.

Treated animals showed increased body weight and food consumption for up to a year of dosing as well as incidence if ataxia, alopecia, tremors, teeth chattering, and increased activity when compared to controls. Clinical chemistry and hematological values were not affected by treatment. No increase in tumors was observed in hamsters given either diazepam or quazepam. Tables showing the distribution of tumor types (both neoplastic and nonneoplastic) are reproduced below.

Spontaneous tumors which occurred appeared with the greatest frequency in the adrenal gland and intestine. There was no compound related increase in the incidence of tumors or change in tumor malignancy. The most frequently occurring tumor was the cortical adenoma, which is a common tumor in the hamster. These tumors as well as intestinal adenocarcinomas (a tumor often associated with enteritis in hamsters) were found to occur equally between sexes and were distributed among treated and control groups in random fashion. The following microscopic changes were observed and were believed to be compound-related, occurring primarily at the high dose level of either quazepam or diazepam: (liver) hemorrhagic necrosis, hepatocellular regeneration, hepatocytomegaly, cytoplasmic pigmentation, extramedullory hematopoiesis. Also observed were gallbladder edema, subcapular spindle cell hyperplasia and cortical pigmentation in the adrenal gland, and atrial thrombosis in the heart. The incidence of these findings was variable but statistically significantly greater at high dose than in controls.

The general conclusion is that quazepam is not carcinogenic in hamsters at doses ranging from 5 to 200 times the maximum proposed human dose of 0.6 mg/kg. The following pages contain the sponsor's tables of tumor incidence and type.

18-MONTH ONCOGENITY STUDY OF SCH 16134 IN HAMSTERS

FREQUENTLY OCCURRING NON-NEOPLASTIC LESIONS

LESION		CONTROL	DIAZEPAM (150 mg/kg)	SCH 16134 (mg/kg) 3	20	120
HEPATOCYTES/PIGMENT	M	2/112	56/56[a]	45/54[a]	55/56[a]	51/56[a]
	F	4/112	54/56[a]	10/56[a]	22/56[a]	53/56[a]
HEMORRHAGIC NECROSIS	M	0/112	15/56[a]	2/54	6/56[a]	26/56[a,d]
	F	1/112	5/56[b]	1/56	2/56	21/56[a,c]
HEPATOCELLULAR REGENERATION	M	0/112	7/56[a]	3/54[b]	6/56[a]	15/56[a]
	F	1/112	0/56	0/56	2/56	11/56[a,c]
HEPATOCYTOMEGALY	M	4/112	26/56[a]	7/54[b]	15/56[a]	48/56[a,c]
	F	5/112	14/56[a]	7/56	3/56	25/56[a,d]
EDEMA OF GALLBLADDER	M	5/103	9/54[b]	7/45[b]	5/51	8/51[b]
	F	4/104	2/54	0/50	2/50	12/49[a,c]
ADRENAL HYPERPLASIA	M	62/112	39/55	24/55	26/55	41/56[b]
	F	14/112	30/56[a]	1/56	8/55	34/55[a]
ADRENAL PIGMENT	M	67/112	44/55[a]	39/55	35/55	48/56[a]
	F	15/112	37/56[a]	1/56	4/55	43/55[a]
ATRIAL THROMBOSIS	M	13/112	17/56[a]	8/55	7/56	25/56[a,d]
	F	30/112	9/56	12/56	8/56	19/56
EXTRAMEDULLARY HEMATOPOEISIS LIVER	M	7/112	9/56[b]	5/54[b]	12/56[a]	19/56[a,d]
	F	1/112	4/56[b]	4/56[b]	7/56[a]	13/56[a,d]
SPLEEN	M	41/112	21/56	19/54	28/56	30/56[b]
	F	46/112	21/56	23/56	18/56	29/56

a = $P \leq 0.01$ compared to Control

b = $P \leq 0.05$ compared to Control

c = $P \leq 0.01$ compared to Diazepam

d = $P \leq 0.05$ compared to Diazepam

Statistical evaluation of data was performed by Schering Corporation, Lafayette, NJ.

NEOPLASTIC LESIONS IN HAMSTERS

Organ/ Tumor Type	Sex	Incidence/# Observed Animals Control	Diazepam (120 mg/kg)	Quazepam (mg/kg) LD (3)	MD (20)	HD (120)
Spleen						
malignant lymphoma	M	4/112	1/53	2/53		
	F	3/111				
reticulam cell screen	F	2/111	3/35	1/35	1/55	2/52
Pancreas						
islet cell adenoma	M		2/54			
Esophagus						
malignant lymphoma	M	2/10				
Lung						
malignant lymphoma	M	6/12				
	F	2/111				
Liver						
malignant lymphoma	M	5/112				
	F	3/111				
reticulam cell sarcoma	M	1/112				
	F		2/56			
Ileum						
malignant lymphoma	M	2/103				
adenocarcinoma	M	2/103		1/44		
Cecum						
adenocarcinoma	M	1/108	2/53	3/50	4/54	1/55
	F	2/105			2/53	4/54
Mesenteric Lymph Node						
metastatic adenocarcinoma	F	4/105	1/53	1/42	4/52	2/49
Bone Marrow (sternum)						
malignant lymphoma	M	6/111				
Lymph Node (cervical)						
malignant lymphoma	M	5/103				
reticulam cell sarcoma	F	1/108	2/55			
Bone (femur)						
malignant lymphoma	M	5/110				
Adrenal						
cortical adenoma	M	15/112	11/55	15/55	9/55	9/56
	F	5/112	2/56		2/55	5/55
cortical carcinoma	M	1/112		1/55	1/55	1/56
malignant lymphoma	M	1/112	1/55		1/55	
pheochromocytoma	M					3/56

NDA 18-708

Quazepam Carcinogenicity Study in Mice - 18 Months

Animal: CD-1 albino mice

Dose: 0, 30, 60, 120 mg/kg p.o. daily

and sec per group: 55M, 55F tested. Control = 105M, 105F

Duration: 18 months intended with males getting an extra 13 weeks

The mouse was selected as the test species in this study because pharmacological activity and proof of absorption of drug by mice had been demonstrated and the mouse is an accepted animal model for carcinogenicity studies.

Survival

Most of the intercurrent deaths occurred after 52 weeks of dosing.

		Dose mg/kg			
		0	30	60	120
males	percent mortality: at 52 weeks	9	14	20	8
	percent mortality: at 91 weeks	57	62	50	44
females	percent mortality: at 52 weeks	5	6	2	4
	percent mortality: at 79 weeks	42	52	52	62

The mice were observed daily for changes from normal physical appearance and behavior. Each mouse was palpated weekly for tissue masses. Plasma concentrations of quazepam were monitored during the study. Microscopic examination was performed on all tissues from mice that died during the study, from all control and high dose mice at termination, and on selected tissues from low and mid-dose mice.

NDA 18-708

Refer to the table below for incidence of tumors. Postmortem examination of animals which died or were sacrificed during this study or at the terminal necropsy revealed no drug-related changes. Nodules and masses occurred most frequently in the lungs, liver, kidneys, and lymph nodes, and were equally distributed across all groups. The most common incidental changes observed in all groups included: emaciation, inflammatory changes, congestion, atrophy or dilatation of organs, uroliths in the urinary tract, alopecia, and bone fracture.

No-drug related effect upon total tumor incidence or the number of tumor bearing mice was observed. The most frequently observed tumors were adenoma of the liver and lung, and tumors of lymphoreticular tissue. Adenoma of the liver occurred more frequently in males. Tumors of lymphoreticular tissue occurred more frequently in females and adenomas of the lung were equally distributed between the sexes. No study was made concerning the effect of the drug on latency of tumor appearance. There was discussion of which types of observed tumors are actually common to the aging mouse, such as amyloid in the zona reticulosis of the adrenals, the villi of the intestine, the renal glomerula, and around the hepatic veins of all groups including the control.

An increase in the incidence of amyloid in adrenals, G.I. tract, and kidneys of the HD males was observed (see table below). While there was an increase in the incidence of amyloid in the liver of MD females, there was no increase seen in the HD group. It is difficult to attach any toxicological signficance to this finding. There did seem to be a dose-related increase in yellowish brown pigment in the cytoplasm of hepatocytes of treated mice. Considering all of the evidence of this study it appears that quazepam is not oncogenic in the mouse.

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TABLE
18-MO[NTH] [CARC]INOGENICITY STUDY OF SCH 16131 IN MICE

INCID[ENCE] OF AMYLOID AN[D] YELLOW-BROWN PIGMENT

	DOSE LEVELS (mg/kg)							
	0		30		60		120	
OBSERV[ATIONS]	M	F	M	F	M	F	M	F
ADRENA[L]								
Amyl[oid] [dep]osis	6/99	47/98	3/50	26/50	6/50	28/49	14/50*	26/50
Dege[ne]ration, bro[wn]	72/99	21/98	30/50	17/50	12/50	10/49	1/50	10/50
Prol[if]eration, sub[cap]sular	61/99	72/98	23/50	28/50	18/50	25/49	27/50	24/50
G.I. T[RACT], AMYLOIDOSIS								
Duod[enum]	1/98	38/97	2/50	20/48	2/49	19/48	9/49*	25/49
Ileu[m]	1/99	41/97	6/50	27/49	8/49	20/49	16/49*	23/49
Jej[unum]	2/99	41/97	8/50	33/49	11/49	33/49	17/49	31/49
KIDNEY								
Amyl[oid] [dep]osis	16/100	47/98	4/50	29/50	6/50	27/50	14/50*	28/50
LIVER								
Amyl[oid] [dep]osis	6/100	12/98	6/50	16/50	1/50	19/50*	2/50	16/50
Yell[ow-]brown Pig[ment]	25/100	26/98	16/50	15/50	23/50*	23/50*	42/50*	31/50*

* Stat[istic]ally significant p≤0.05.

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LE 1
MONTH MICRONUCLEUS STUDY OF NCR 1611 IN MICE

SARY TABLE: [illegible]

E PL /KG)	NO. MICE /GROUP/ SEX	TOTAL OR CHED. DEATHS MALES	FEMALES	WEEK OF 50% MORTALITY MALES	FEMALES	NO. KILLED AT TERM. NECROPSY MALES	FEMALES	WEEK OF TERM NECROPSY MALES	FEMALES	% SURVIVORS TERM. NECROPSY MALES	FEMALES	% MORTALITY UNSCHED. DEATHS MALES	FEMALES
0 (control)	100	57	42	89	79[b]	43	58	91	79	43	58	57	42
30 H 1611(+)	50	31	26	84	77	19	24	91	79	38	48	62	52
60 H 1611(+)	50	25	26	90	75	25	24	91	79	50	48	50	52
120 H 1611(+)	50	22	32	91[c]	68	28	18	91	79	56	36	44	64

[illegible] not include [illegible] study absorption of test substance
[illegible] mortality at terminal necropsy
[illegible] mortality at [illegible] necropsy

TABLE 7
18-MONTH ONCOGENICITY STUDY OF SCH 16134 IN MICE

DISTRIBUTION OF TUMORS IN MICE: PREFACE

CLASSIFICATION OF NEOPLASMS OF LYMPHORETICULAR TISSUE

The histopathologic classification of Dunn (J. Nat. Cancer Inst. 14, 1281, 1954) was used for the neoplasias of the lymphoreticular tissue.

Lymphocytic neoplasms refer to neoplasms composed of uniform cells resembling normal lymphocytes but at times showing clear indented vesicular nuclei, prominent nucleoli and pale blue cytoplasm.

Neoplasm Type A: The reticulum-cell neoplasms Type A are composed of a single cell type, the monocyte or histiocyte. This cell shows various size and degree of phagocytic activity characterized by a foamy appearance and by the presence of phagocytized debris or hemosiderin.

Neoplasm Type B: The reticulum-cell neoplasms Type B have a pleomorphic structure showing basophilic mononuclear cells intermingled with plasma cells, a few granulocytes and occasional multinucleated cells and eosinophils. Dunn refers to this neoplasm as the "Hodgkin's-like lesion."

Neoplasm Type C: The reticulum-cell neoplasms Type C are composed of pale-staining fusiform cells arranged in masses or trabeculae bordered by lymphocytes. These features resemble a chronic granulomatous process in man such as Boeck's sarcoid or tuberculosis without, however, asteroid bodies, necrosis or multinucleated cells.

TABLE 7
18-MONTH ONCOGENICITY STUDY OF SCH 16134 IN MICE

DISTRIBUTION OF TUMORS IN MICE: WEEKS 1 - 91

OBSERVATIONS	DOSE LEVELS (mg/kg)							
	0		20		60		[illegible]	
	M	F	M	F	M	F	M	F
ADRENALS								
Adenoma	2							
BONE								
Hemangiosarcoma					1			
Osteoma		1						
DUCTUS DEFERENS								
Hemangioma			1					
EPIDIDYMIDES								
Lipoma	1							
HARDERIAN GLANDS								
Adenoma	2							
JEJUNUM								
Lipoma		1						
LACRIMAL GLANDS								
Adenoma						1	1	
LIVER								
Adenoma	13		3	1	5	2	9	2
Carcinoma	1							
Hemangioma		1				1		
[illegible]								
Adenocarcinoma	1		1					
Adenoma	13	7	6		4	1	4	
[illegible]								
Hemangiosarcoma (Spleen)			1	1		1	1	
[illegible] Granulocytic	1							
Lymphocytic Neoplasm		9	1	5		3	1	2
Neoplasm Type A	3	3		2		1		
Neoplasm Type B		6	1	1		2	1	2
Neoplasm Type C								

TABLE 7
18-MONTH ONCOGENICITY STUDY OF SCH 16134 IN MICE

DISTRIBUTION OF TUMORS IN MICE: WEEKS 1 - 91

OBSERVATIONS	DOSE LEVELS (mg/kg) 0 M	0 F	30 M	30 F	60 M	60 F	120 M	120 F
MAMMARY GLAND								
Carcinoma		1						
MESOMETRIUM								
Lipoma								1
OVARIES								
Carcinoma				1				
Cystadenoma				2				
Granulosa-Leydig Cell Tumor		12						3
Thecoma								1
PANCREAS								
Adenoma		1						
PITUITARY								
Adenoma		2						
RECTUM								
Adenomatous Polyp						1		
SKIN, SUBCUTANEOUS TISSUE								
Adenoma, Sebaceous								1
Hibernoma		1						
TAIL								
Fibroma				1				
THYROID								
Adenoma		1						
UTERUS								
Carcinoma				1				1
Fibroma				1				1
Leiomyosarcoma				1				
URINARY BLADDER								
Carcinoma		1						
Papilloma		3		1				

TABLE 7
13-MONTH ONCOGENICITY STUDY OF SCH 16134 IN MICE

DISTRIBUTION OF TUMORS IN MICE: WEEKS 1 - 91

OBSERVATIONS	DOSE LEVELS (mg/kg)							
	0		30		60		[illegible]	
	M	F	M	F	M	F	M	F
Number of Tumors	45	54	16	16	10	13	17	28
Tumor Bearers	40 40%	41 41%	13 26%	15 30%	9 18%	13 26%	16 32%	25 50%
Number of Animals	100	98	50	50	50	50	50	50

TABLE 7
13-MONTH ONCOGENICITY STUDY OF SCH 16134 IN MICE

DISTRIBUTION OF TUMORS IN MICE: SCHEDULED SACRIFICES

OBSERVATIONS	DOSE LEVELS (mg/kg) 0 M	0 F	30 M	30 F	60 M	60 F	120 M	120 F
ADRENALS								
Adenoma	2							
DUCTUS DEFERENS								
Hemangioma			1					
EPIDIDYMIDES								
Lipoma	1							
HARDERIAN GLANDS								
Adenoma	2							
JEJUNUM								
Lipoma		1						
LACRIMAL GLANDS								
Adenoma						1		1
LIVER								
Adenoma	9		1	1	2		6	1
LUNGS								
Adenocarcinoma			1					
Adenoma	10	1	3		2	1	3	5
LYMPHORETICULAR SYSTEM								
Hemangiosarcoma (Spleen)						1		
Leukemia, Granulocytic								
Lymphocytic Neoplasm								
Neoplasm Type A								
Neoplasm Type B								
MESENTERIUM								
[illegible]								
[illegible]								
[illegible]								
[illegible]								
[illegible]								
[illegible]								
Adenomatous Polyp								

TABLE 7
18-MONTH ONCOGENICITY STUDY OF SCH 16134 IN MICE

DISTRIBUTION OF TUMORS IN MICE: SCHEDULED SACRIFICES

OBSERVATIONS	DOSE LEVELS (mg/kg)							
	0		30		60		[illegible]	
	M	F	M	F	M	F	M	F
SKIN, SUBCUTANEOUS TISSUE								
Adenoma, Sebaceous				1				
Hibernoma	1							
TAIL								
Fibrosarcoma			1					
THYROID								
Adenoma	1							
UTERUS								
Carcinoma		2		1				
Leiomyoma		1		1				1
Leiomyosarcoma		1						
URINARY BLADDER								
Papilloma			1					
Number of Tumors	27	26	9	5	4	5	11	14
Tumor Bearers	24	23	7	4	4	5	10	11
	56%	35%	35%	16%	16%	22%	36%	61%
Number of Animals	43	66	20	25	25	23	28	18

TABLE 7
18-MONTH ONCOGENICITY STUDY OF SCH 16134 IN MICE

DISTRIBUTION OF TUMORS IN MICE: UNSCHEDULED DEATHS OR SACRIFICE

OBSERVATIONS	DOSE LEVELS (mg/kg)							
	0		30		60		[illegible]	
	M	F	M	F	M	F	M	F
BONE								
Hemangiosarcoma					1			
Osteoma		1						
LIVER								
Adenoma	4		2		3	2	3	1
Carcinoma	1							
Hemangioma		1				1		
LUNGS								
Adenocarcinoma	2							
Adenoma	3	3	3		2		1	1
LYMPHORETICULAR SYSTEM								
Hemangiosarcoma (Spleen)				1			1	
Leukemia, Granulocytic	2	1						2
Lymphocytic Neoplasm		4	1	5		3	1	6
Neoplasm Type A	2	3		2				1
Neoplasm Type B		6	1	1		2		1
Neoplasm Type C								1
MAMMARY GLAND								
Carcinoma					1			
OVARIES								
Cystadenoma								1
Interstitial-Leydig Cell Tumor					1			
UTERUS								
Adenoma					1			
PITUITARY								
[illegible]					-			
UTERUS								
Carcinoma					2			
Leiomyosarcoma					1			
URINARY BLADDER								
Carcinoma	1							
Papilloma	3							

TABLE 7
18-MONTH ONCOGENICITY STUDY OF SCH 16134 IN MICE

DISTRIBUTION OF TUMORS IN MICE: UNSCHEDULED DEATHS OR SACRIFICES

	DOSE LEVELS (mg/kg)							
	0		30		60		120	
OBSERVATIONS	M	F	M	F	M	F	M	F
Number of Tumors	18	28	7	11	6	8	6	14
Tumor Bearers	16 28%	18 56%	6 20%	11 44%	5 20%	8 30%	6 27%	14 44%
Number of Animals	57	32	30	25	25	27	22	32

NCA 18-708

Sponsor's Mutagenicity Report

Quazepam was tested, over a range of concentrations for 2 g/ml to 200 g/ml, in the L5178YTK+/- Mouse Lymphoma Mutagenesis assay with and without exogenous metabolic activation (5-9) by Aroclor induced rat liver microsomes. Non-activated cultures were cloned over a range of 11 to 200 g/ml of quazepam. Several of the cultures exhibited mutant frequencies which were two-fold greater than solvent controls. The results of this study show that the test article may have induced a positive response. For the 5-9 activated cultures cloned over a concentration range of 2-47 g/ml, only the two highest treated cultures 36 and 47 g/ml showed mutant frequencies which were greater than twice control. The Ames test was negative.

OVERALL SUMMARY AND EVALUATION

Quazepam is a hypnotic agent related structurally to flurazepam and diazepam. The sponsor proposes that the drug be marketed for the treatment of all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings. The drug is to be marketed in 15 and 30 mg tablets with the daily recommended dosage of 0.6 mg/kg or 30 mg daily for the 50 kg human. Relevant animal studies performed include acute and chronic toxicity in the hamster and squirrel monkey, reproduction studies using the mouse and rabbit, carcinogenicity studies in the mouse and hamster, and other appropriate studies of pharmacological activity, drug metabolism, mutagenicity, etc.. Pilot studies showed quazepam to be largely inactive in the rat because, although well absorbed orally, quazepam is rapidly metabolized and excreted in the rat. Thus, tissue levels of the drug sufficient to cause pharmacological effect in that species cannot be achieved. The hamster was selected for the long term rodent testing because that animal responded to the toxicologic and pharmacologic properties of quazepam and because studies showed that the hamster metabolized quazepam in a manner similar to that found in man.

The main behavorial effects of quazepam in animals are drowsiness and sedation. Quazepam was found to be twice as potent as flurazepam and half as potent as lorazepam in hypnotic activity measured using the eye closure test in monkeys. Studies of the dependence potential of Quazepam produced results which suggest a profile similar to that of marketed benzodiazepine (this is further elaborated upon in a consulting review from the Drug Abuse Unit). Like diazepam and flurazepam, quazepam potentiated the ethanol-induced loss of righting reflex in mice. Quazepam produced no significant changes in blood pressure, heart rate, or EKG in the unanesthetized dog while doses (60 mg/kg) large enough to cause ataxia and sedation were used.

Quazepam is well absorbed by the mouse, rat, hamster, squirrel, monkey, and man when given orally. It is almost totally metabolized and extensively so on first pass. Four pharmacologically active metabolites have been identified. The plasma half-life of quazepam is about 40 hours in man. Quazepam penetrates the placental barrier, and does so more readily near term than at embryonic states. Quazepam and its metabolites are excreted in urine and feces, mostly within 24 hours of administration. The drug is a weak inducer of hepatic drug metabolizing enzymes in the hamster.

Signs of acute toxicity of quazepam in animal studies included hypoactivity, deep respiration, ptosis, head shaking, ataxia, and straub tail in mice. Long term toxicity studies were performed using the hamster (1 year) and squirrel monkey (1 year).

The hamster study used doses of drug which ranged from 5 to 200 times the maximum proposed human dose of 0.6 mg/kg (i.e., 0, 3, 20, 120 mg/kg/day). One group of hamsters was treated with diazepam (120 mg/kg) for comparison. Mortality among the hamster was evenly divided between dosed and control groups, and was attributed to enteritis, atrial thrombosis, and heart failure, or renal amyloidosis and uremia. The conditions were regarded as spontaneous and not drug related. Both diazepam and quazepam elicited ataxia, alopecia, tremors, and hyperactivity at the high dose level. While neither drug altered water consumption, both drugs were associated with enhanced body weight and food consumption in the HD males. The drugs did not alter hematology or clinical chemistry values. Bile retention was the only significant finding by histopathology and occurred at HD for both drugs. The dose range employed was sufficient both to demonstrate evidence of toxicity and allow for acceptable long term survival of the animals.

The requirement for long term testing in a non rodent test animal was approached with a one year study using the squirrel monkey. Doses of 2, 10, and 50 mg/kg were employed as was a 50 mg/kg diazepam control dose. The quazepam doses were 3, 17, and 83 times the proposed maximum human dose. Both drugs produced sedation, somnolence, ataxia, and tremors. No compound related effects could be determined from hematology, blood chemistry, and urinalysis. The doses of drug employed were sufficient to allow adequate survival rates while stll showing pronounced pharmacological effect.

Reproduction studies were conducted using the mouse and rabbit. Doses were used in the Segemnt I mouse study which correspond to 20, 60, and 180 times the proposed human dose. There was a dose-related reduction in number of pregnancies (0 at low dose, 20% at medium dose, and 30% at high dose), increase in number of embryoic deaths, increased post-implantation loss (17% at high dose versus 6.7% for control), and increased pup loss. The drug did not affect duration of gestation. Some of the pups that survived showed retarded development. The teratology study in the mouse showed some instances of retarded bone ossification which could be considered drug related, but only at the high dose. Teratology studies in the rabbit did not reveal any evidence that ~~flurazepam~~ Quazepam would be a teratogen in that species.

Carcinogenicity studies were performed using the hamster and the mouse. Incidence of lesions were analyzed using Fisher's Exact test , F-MAX, ANOVA, Dunnett's test, and the Behren-Fisher t-test. In the mouse, nodules and masses occurred most frequently in the lungs, liver, kidneys, and lumph nodes, and were equally distributed across all groups. No drug-related effect upon total tumor incidence or the number of tumor-bearing mice was observed. The most frequently observed tumors were adenoma of the liver and lung, and tumors of lymphoreticular tissue. Taken as a whole, the mouse data do not present evidence for quazepam carcinogenicity in that species. The 18 month carcinogenicity study using the hamster, employed doses of quazepam approximately 5, 33, and 200 times the proposed maximum human dose. Of the initial number of hamsters in each group, half of the males survived to 55-56 weeks while half of the females survived to 46-55 weeks. No increase in tumors was observed in hamsters given either diazepam and quazepam. Spontaneous tumors which occurred appeared with the greatest frequency in the adrenal gland and intestine. There was no compound-related increase in the incidence of tumors or change in tumor malignancy. The most frequently occurring tumor was the cortical adenoma, a common tumor in the hamster. These tumors as well as intestinal adenocarcinomas (a tumor often associated with enteritis in hamsters) were found to occur equally between sexes and were distributed among treated and control groups in random fashion. The data generally did not support a role for quazepam as a carcinogen in the hamster.

RECOMMENDATIONS:

I recommend that the application be approved from the preclinical animal toxicity viewpoint. In my evaluation of the toxicity data I could not find grounds for refusing to approve. The application appears to contain adequate preclinical tests by all means reasonably applicable to show whether or not the drug is safe to use under the conditions in the labeling. The proposed labeling, in my view, is not false or misleading regarding preclinical study results.

Robert Hollenbeck

Robert Hollenbeck, Ph.D.
Reviewing Pharmacologist

Orig. NDA 18-708
HFN-120
HFN-120/RHollenbeck
JContrera/6-13-85
HFN-180
HFN-102/Glocklin
F/T:GD/6-18-85
Doc. 0095f

Medical Officer's Review of NDA 16-738
(Original Submission: April 8, 1982)

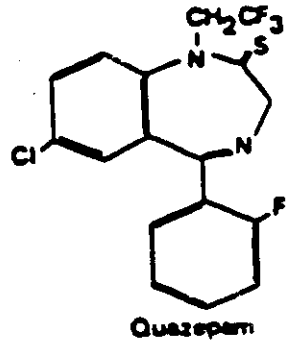
Sponsor: Schering Corporation
Bloomfield, NJ

8 1985

Name of Drug:

Code designation: SCh 16134
USAN: quazepam (Q)
Trade name: not yet available
Chemical: 7-chloro-5 (o-fluorophenyl)-1,3-dihydro-1-(2,2,2-trifluoroethyl-2H-1,4-benzodiazepin-2-thione)

Structural Formula:



Quazepam

Pharmacologic Category: benzodiazepine hypnotic

Dosage Forms: quazepam 15 mg tablets

Route of Administration: oral

Related IND: ———

Chemist's Review (V. Iliev, Ph.D., 6/6/82): Approval recommended from standpoint of manufacturing controls.

Pharmacology (Refer to review by R. Hollenbeck, Ph.D., of 10/14/82):

The main behavioral effect of quazepam in animals is drowsiness and sedation. The reviewing pharmacologist recommends that the application for quazepam be approved.

Review of Bioavailability Studies [refer to review of 5/26/83 by N.E. Useene, Ph.D. (HFN-525)]:

The application is acceptable to the Division of Biopharmaceutics, if the firm agrees to further dissolution testing as outlined in the final section of recommendations.

Pharmacokinetic profile:

Quazepam is rapidly absorbed from the G.I. tract. The plasma concentrations of quazepam are proportional to the administered dose; peak levels of approximately 20 ng/ml after a 15 mg dose and 40 ng/ml after a 30 mg dose are obtained at about 2 hrs.

Quazepam is extensively metabolized; two major plasma metabolites, 2-oxoquazepam (formed by the substitution of oxygen for sulfur) and N-desalkylflurazepam (formed by the N-dealkylation of 2-oxoquazepam) are pharmacologically active.

The elimination half-life of quazepam or 2-oxoquazepam is about 40 hours and that of N-desalkylflurazepam is about 70 hours. After multiple-dosing, the observed steady-state levels of quazepam and 2-oxoquazepam are attained by the seventh daily dose and that of N-desalkylflurazepam by the thirteenth daily dose.

The elimination half-life of N-desalkylflurazepam in geriatric patients is about twice that of young adults.

Quazepam, 2-oxoquazepam and N-desalkylflurazepam are present in breast milk of lactating women.

Drug Abuse Consulting Review [refer to review of 5/3/83 by F.J. Vocci, Jr., Ph.D. (HFN-123)]:

The sponsor has not demonstrated that quazepam is significantly different from other benzodiazepines with respect to abuse potential.

Clinical doses, up to 30 mg a night for 4 weeks, do not produce a significant withdrawal syndrome.

On April 26, 1983, the Drug Abuse Advisory Committee agreed that quazepam be placed in Schedule IV of the Controlled Substances Act.

I. Controlled Clinical Studies

A. Sleep Lab Studies:

C&O-077-01 (in volume 1.36): by Gerald W. Vogel, Director, Sleep Lab, GAMHI, Atlanta.

Objective: to evaluate the short-term (5 nights) safety, and relative efficacy of quazepam (Q) 15 mg and 30 mg and flurazepam (F) 15 mg and 30 mg in volunteers with chronic insomnia.

Experimental Design:

The study involved a parallel group design in which treatment was administered in a double-blind fashion to 24 healthy subjects (8 men and 16 women), ages 24 to 60 yrs, with both subjective and objective insomnia. Subjects complained of taking 45 minutes or more to fall asleep and sleeping for fewer than 6.5 hours at least 4 nights/week for 3 months or more prior to the pre-treatment interview. Objective insomnia was measured during nights 2-4 in a four consecutive night placebo baseline; TST of less than 400 minutes in 450 minutes of total bedtime on any two of baseline nights 2-4.

Schedule was as follows:

Night 1: placebo (adaptation to sleep lab)
Night 2-4: placebo (baseline)
Night 5-9: drug (either Q15, Q30, F15 or F30 mg)
Night 10-11: placebo (drug withdrawal)

24 subjects were randomly assigned to 4 treatment groups (6/group).

Measurements:

The following polygraphic efficacy variables were scored:

1. TST (total sleep time)
2. % sleep (% of total bedtime occupied by sleep)
3. TWT (total wake time)
4. Wake time in each third of the night
5. Persistent sleep latency (time from "lights out" to the onset of the first sleep that persisted for at least 10 consecutive minutes)
6. Wake time after persistent sleep onset
7. Number of awakenings $\geq$ 30 seconds duration

Efficacy and safety were assessed both within and between treatment groups.

Results: (refer to following tables in Volume 1.36)

#2 (p.104)
" (p.105)
" (p.106)
" (p.107)
" (p.108)
" (p.109)
" (p.110)
" (p.113)
" (p.114)

TABLE # 2
PAGE 1

QUAZEPAM STUDY 3

POLYGRAPHIC EFFICACY VARIABLE - ACROSS ALL SUBJECTS

TOTAL SLEEP TIME (MINUTES)

S#	BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN
	QUAZEPAM 15mg.				
1	344.2	423.5	427.7	425.5	427.0
2	377.7	432.5	437.1	437.0	430.8
3	369.2	371.5	322.2	397.5	407.0
4	397.0	413.0	403.9	385.0	401.0
5	401.0	390.5	386.4	428.0	421.2
6	380.0	399.5	400.4	405.5	383.5
MN	377.5	405.1	396.3	413.1	411.8
P(diff. from BSL)		**	NS	**	**
S#	FLURAZEPAM 15mg.				
13	380.3	397.5	399.6	405.0	386.0
14	361.5	403.0	402.0	387.5	373.0
15	399.7	412.5	417.6	417.0	417.5
16	374.3	395.5	391.6	410.0	412.2
17	402.0	437.0	427.8	422.5	425.2
18	375.7	393.0	413.0	367.0	380.8
MN	382.2	407.1	408.6	401.5	399.1
P(diff. from BSL)		***	***	**	**

S#	BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN
	QUAZEPAM 30mg.				
7	321.2	405.0	426.9	420.0	416.2
8	389.5	429.5	428.2	429.0	429.0
9	362.7	404.0	385.8	396.5	391.2
10	365.8	427.0	435.8	442.0	433.8
11	330.8	372.5	380.1	394.0	404.0
12	385.0	434.0	413.1	423.5	424.0
	359.2	412.0	411.6	417.5	416.4
		***	***	***	***
S#	FLURAZEPAM 30mg.				
19	335.3	283.0	398.6	420.0	423.5
20	327.2	429.5	420.5	389.5	339.5
21	327.0	352.0	365.1	357.5	364.0
22	359.2	358.0	356.5	391.5	376.5
23	357.8	373.0	370.9	412.0	409.2
24	370.8	404.5	407.5	383.5	361.5
	346.2	366.7	386.5	375.7	379.0
		NS	**	NS	*

P(difference between QUAZEPAM change from BSL. and FLURAZEPAM change from BSL.)
(The BSL MEAN entries represent P(diff. between Q BSL and F BSL))

	BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN
15mg	NS	NS	NS	NS	NS
30mg	NS	NS	NS	NS	NS

Within treatment differences assessed by matched pair t-test, one tailed for baseline vs drug, two tailed for baseline vs post drug. Across treatment difference assessed by two tailed, non-paired t-test.

KEY:

NS Not Significant at 0.10 level
* Probability < 0.10
** Probability < 0.05
*** Probability < 0.01

TABLE # 2
PAGE 2

QUAZEPAM STUDY 3

POLYGRAPHIC EFFICACY VARIABLE - ACROSS ALL SUBJECTS

PERCENT SLEEP

S#	BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN	S#	BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN
	QUAZEPAM 15mg.						QUAZEPAM 30mg.				
1	76.5	94.1	95.0	94.6	94.9	7	71.4	89.9	94.8	93.3	92.5
2	84.2	96.1	97.1	97.1	95.7	8	86.5	95.1	95.1	95.3	95.3
3	81.1	82.6	71.6	88.3	90.4	9	80.6	89.8	85.7	88.0	86.9
4	88.2	91.8	89.7	85.6	89.1	10	81.1	94.9	96.8	98.2	96.4
5	89.1	86.8	85.9	95.1	93.6	11	73.6	82.8	84.5	87.6	89.8
6	84.4	88.8	89.0	90.1	85.2	12	85.6	96.4	91.3	94.0	94.2
MN	83.9	90.0	88.1	91.8	91.5		79.8	91.5	91.5	92.7	92.5
P(diff. from BSL)		**	NS	**	**			***	***	***	***
S#	FLURAZEPAM 15mg.					S#	FLURAZEPAM 30mg.				
13	84.5	88.4	88.8	90.0	85.8	19	74.5	62.9	88.6	93.3	94.1
14	80.3	89.4	89.3	86.1	82.9	20	72.7	95.4	93.4	64.3	75.4
15	88.8	91.7	92.8	92.7	92.8	21	72.7	78.2	81.2	79.4	80.9
16	83.1	88.5	87.0	91.1	91.6	22	79.8	79.6	79.2	87.0	83.7
17	89.3	97.1	95.1	93.9	94.5	23	79.5	82.9	82.4	91.6	90.9
18	83.5	87.3	91.8	81.6	84.6	24	82.4	89.9	90.6	85.2	80.3
MN	84.9	90.4	90.8	89.2	88.7		76.9	81.5	85.9	83.5	84.2
P(diff. from BSL)		***	***	**	**			NS	**	NS	*

P(difference between QUAZEPAM change from BSL. and FLURAZEPAM change from BSL.)
(The BSL MEAN entries represent P(diff. between Q BSL and F BSL))

	BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN		BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN
15mg	NS	NS	NS	NS	NS	30mg	NS	NS	NS	NS	NS

Within treatment differences assessed by matched pair t-test, one tailed for baseline vs drug, two tailed for baseline vs post drug. Across treatment difference assessed by two tailed, non-paired t-test.

KEY:

NS Not Significant at 0.10 level
* Probability < 0.10
** Probability < 0.05
*** Probability < 0.01

TABLE # 2
PAGE 3

QUAZEPAM STUDY 3

POLYGRAPHIC EFFICACY VARIABLE - ACROSS ALL SUBJECTS

TOTAL WAKE TIME (MINUTES)

S#	BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN	S#	BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN
	QUAZEPAM 15mg.						QUAZEPAM 30mg.				
1	102.3	22.0	17.0	22.0	20.5	7	127.7	45.0	21.4	24.5	30.0
2	66.0	13.5	10.7	11.0	16.5	8	52.8	12.0	15.5	14.5	15.0
3	80.0	72.5	122.6	45.0	32.8	9	81.0	33.5	56.9	49.5	53.0
4	49.7	30.0	40.1	61.0	43.8	10	81.8	17.0	10.4	7.0	14.5
5	47.5	58.0	60.5	13.0	22.8	11	114.2	72.5	66.2	53.5	43.5
6	66.0	44.0	42.5	37.0	60.2	12	59.7	10.5	33.5	24.5	23.2
MN	68.6	40.0	48.9	31.5	32.8		86.2	31.9	34.0	28.9	29.9
P(diff. from BSL)		**	NS	**	**			***	***	***	***
S#						S#					
	FLURAZEPAM 15mg.						FLURAZEPAM 30mg.				
13	68.3	50.5	49.2	42.5	62.2	19	113.5	166.0	49.5	26.0	23.8
14	88.3	46.5	47.6	62.5	76.2	20	116.7	16.5	27.1	155.0	104.5
15	43.5	31.0	25.2	26.5	21.5	21	122.5	94.0	82.7	90.5	85.0
16	72.0	50.0	54.6	37.0	32.0	22	88.8	91.0	91.0	56.5	71.0
17	44.7	10.5	19.7	21.5	20.5	23	90.2	71.0	75.5	36.5	38.5
18	73.0	57.0	35.3	77.5	65.0	24	75.8	42.0	39.0	63.0	65.8
MN	65.0	40.9	38.6	44.6	46.2		101.2	80.1	60.8	71.2	68.1
P(diff. from BSL)		***	***	**	**			NS	**	NS	*

P(difference between QUAZEPAM change from BSL. and FLURAZEPAM change from BSL.)
(The BSL MEAN entries represent P(diff. between Q BSL and F BSL))

	BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN		BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN
15mg	NS	NS	NS	NS	NS	30mg	NS	NS	NS	NS	NS

Within treatment differences assessed by matched pair t-test, one tailed for baseline vs drug, two tailed for baseline vs post drug. Across treatment difference assessed by two tailed, non-paired t-test.

KEY:

NS	Not Significant at 0.10 level
*	Probability < 0.10
**	Probability < 0.05
***	Probability < 0.01

TABLE # 2
PAGE 4

QUAZEPAM STUDY 3

POLYGRAPHIC EFFICACY VARIABLE - ACROSS ALL SUBJECTS

WAKE TIME (MINUTES) DURING FIRST THIRD OF NIGHT

S#	BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN	S#	BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN
	QUAZEPAM 15mg.						QUAZEPAM 30mg.				
1	68.2	8.5	6.2	4.5	5.5	7	96.0	29.0	10.8	8.0	9.5
2	20.0	11.5	6.3	3.5	4.8	8	25.5	6.0	8.7	5.0	6.8
3	67.3	69.0	102.3	41.5	29.2	9	68.2	30.0	43.1	30.5	15.8
4	21.2	26.0	32.0	37.0	29.5	10	47.5	17.0	8.8	4.0	9.8
5	20.3	37.5	20.3	4.5	6.8	11	91.3	65.0	63.1	48.0	25.0
6	19.8	9.5	7.8	8.0	11.8	12	24.5	10.5	8.1	10.5	9.0
MN	36.1	27.0	29.2	16.5	14.6		58.8	26.2	23.8	17.7	17.6
P(diff. from BSL)		NS	NS	NS	*			***	**	**	**
S#						S#					
	FLURAZEPAM 15mg.						FLURAZEPAM 30mg.				
13	19.8	25.0	23.7	22.0	18.2	19	53.8	43.0	14.3	8.5	5.2
14	60.5	26.0	25.4	25.5	43.8	20	37.5	5.0	9.1	36.5	23.5
15	24.0	24.5	20.1	13.0	12.2	21	83.0	76.0	64.0	74.5	60.0
16	52.0	15.0	19.4	10.5	9.8	22	29.7	29.5	30.7	22.0	34.8
17	44.5	10.5	18.6	20.5	19.2	23	46.2	59.5	66.9	15.0	16.2
18	36.2	20.5	18.6	50.5	47.0	24	55.2	33.5	27.9	28.5	50.8
MN	39.5	20.2	21.0	23.7	25.0		50.9	41.1	35.5	30.8	31.8
P(diff. from BSL)		**	**	NS	NS			*	*	**	*

P(difference between QUAZEPAM change from BSL. and FLURAZEPAM change from BSL.)
(The BSL MEAN entries represent P(diff. between Q BSL and F BSL))

	BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN		BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN
15mg	NS	NS	NS	NS	NS	30mg	NS	**	NS	NS	NS

Within treatment differences assessed by matched pair t-test, one tailed for baseline vs drug, two tailed for baseline vs post drug. Across treatment difference assessed by two tailed, non-paired t-test.

KEY:

NS	Not Significant at 0.10 level
*	Probability < 0.10
**	Probability < 0.05
***	Probability < 0.01

TABLE # 2
PAGE 5

QUAZEPAM STUDY 3

POLYGRAPHIC EFFICACY VARIABLE - ACROSS ALL SUBJECTS

WAKE TIME (MINUTES) DURING MIDDLE THIRD OF NIGHT

S#	BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN	S#	BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN
	QUAZEPAM 15mg.						QUAZEPAM 30mg.				
1	10.2	2.5	2.2	8.0	6.5	7	6.7	9.5	4.5	8.5	5.0
2	.5	1.0	.4	.0	.0	8	18.5	6.0	4.0	4.5	3.2
3	7.5	1.0	17.8	2.5	3.0	9	7.5	2.5	5.9	16.0	14.2
4	3.3	2.5	3.5	16.0	9.2	10	6.3	.0	.6	.0	2.2
5	10.8	7.5	24.8	.0	3.5	11	7.2	5.0	1.9	2.0	3.8
6	11.2	12.0	6.1	16.5	8.2	12	9.7	.0	14.6	.0	6.0
MN	7.2	4.4	9.1	7.2	5.1		9.3	3.8	5.2	5.2	5.8
P(diff. from BSL)		*	NS	NS	NS			**	*	NS	NS
	FLURAZEPAM 15mg.						FLURAZEPAM 30mg.				
13	26.0	6.5	6.5	14.0	37.8	19	18.3	61.0	15.1	8.0	11.0
14	8.2	15.5	13.1	5.5	4.8	20	68.7	.0	2.3	1.5	4.3
15	4.5	3.5	3.2	6.0	3.5	21	27.3	8.5	8.3	5.5	9.2
16	8.5	22.5	18.0	21.5	18.0	22	7.0	42.5	24.9	23.5	14.8
17	.2	.0	.0	1.0	.5	23	25.2	2.0	3.6	1.0	6.8
18	17.8	10.5	5.8	6.5	4.0	24	10.3	6.0	7.3	34.0	20.2
MN	10.9	9.8	7.8	9.1	11.4		26.1	20.0	10.2	12.2	11.1
P(diff. from BSL)		NS	NS	NS	NS			NS	NS	NS	NS

P(difference between QUAZEPAM change from BSL. and FLURAZEPAM change from BSL.)
(The BSL MEAN entries represent P(diff. between Q BSL and F BSL))

	BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN		BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN
15mg	NS	NS	NS	NS	NS	30mg	NS	NS	NS	NS	NS

Within treatment differences assessed by matched pair t-test, one tailed for baseline vs drug, two tailed for baseline vs post drug. Across treatment difference assessed by two tailed, non-paired t-test.

KEY:

NS	Not Significant at 0.10 level
*	Probability < 0.10
**	Probability < 0.05
***	Probability < 0.01

TABLE # 2
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QUAZEPAM STUDY 1

POLYGRAPHIC EFFICACY VARIABLE - ACROSS ALL SUBJECTS

WAKE TIME (MINUTES) DURING LAST THIRD OF NIGHT

S#	BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN
	QUAZEPAM 15mg.				
1	24.0	11.0	8.6	9.5	8.5
2	45.5	1.0	4.0	7.5	11.8
3	5.2	2.5	2.5	1.0	.5
4	25.2	1.5	4.6	8.0	5.0
5	16.3	13.0	15.4	8.5	12.5
6	39.0	22.5	28.6	12.5	40.2
MN	25.2	8.6	10.6	7.8	13.1
P(diff. from BSL)		**	**	**	*
	FLURAZEPAM 15mg.				
13	22.5	19.0	19.0	6.5	6.2
14	19.7	5.0	9.1	31.5	27.8
15	15.0	3.0	1.9	7.5	5.8
16	11.5	12.5	17.2	5.0	4.2
17	.0	.0	1.1	.0	.8
18	19.0	26.0	10.9	20.5	14.0
MN	14.6	10.9	9.9	11.8	9.8
P(diff. from BSL)		NS	*	NS	NS

S#	BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN
	QUAZEPAM 30mg.				
7	25.0	6.5	6.1	8.0	15.5
8	8.8	.0	2.8	5.0	5.0
9	5.3	1.0	7.9	3.0	3.0
10	28.0	.0	1.0	3.0	2.5
11	15.7	2.5	1.2	3.5	4.8
12	25.5	.0	10.8	14.0	8.2
	18.1	1.7	5.0	6.1	6.5
		***	**	**	**
	FLURAZEPAM 30mg.				
19	41.3	62.0	20.1	9.5	7.5
20	10.5	11.5	15.7	117.0	76.2
21	12.2	9.5	10.4	10.5	15.8
22	52.2	19.0	35.4	11.0	21.5
23	18.8	9.5	5.0	20.5	15.5
24	10.3	2.5	3.8	.5	14.9
	24.2	19.0	15.1	28.2	25.2
		NS	**	NS	NS

P(difference between QUAZEPAM change from BSL. and FLURAZEPAM change from BSL.)
(The BSL MEAN entries represent P(diff. between Q BSL and F BSL))

	BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN
15mg	NS	NS	NS	**	NS
30mg	NS	NS	NS	NS	NS

Within treatment differences assessed by matched pair t-test, one tailed for baseline vs drug, two tailed for baseline vs post drug. Across treatment difference assessed by two tailed, non-paired t-test.

KEY:

NS Not Significant at 0.10 level
* Probability < 0.10
** Probability < 0.05
*** Probability < 0.01

TABLE # 2
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QUAZEPAM STUDY 3

POLYGRAPHIC EFFICACY VARIABLE - ACROSS ALL SUBJECTS

WAKE TIME (MINUTES) AFTER PERSISTENT SLEEP ONSET

S#	BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN	S#	BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN
	QUAZEPAM 15mg.						QUAZEPAM 30mg.				
1	88.8	19.0	14.2	18.0	16.0	7	32.0	16.0	11.0	18.5	22.3
2	48.3	2.0	4.4	7.5	11.8	8	36.0	6.5	9.7	12.0	13.2
3	13.8	3.5	4.3	3.5	3.8	9	13.5	4.0	20.0	29.5	23.8
4	30.0	4.0	9.7	27.0	16.5	10	42.0	10.5	5.2	3.5	5.2
5	29.0	20.5	44.5	10.0	18.0	11	28.7	8.0	5.2	9.0	10.2
6	56.3	35.5	36.8	30.5	54.0	12	48.5	3.5	28.8	20.0	18.2
MN	44.4	14.1	19.0	16.1	20.0		33.4	8.1	13.3	15.4	15.5
P(diff. from BSL)		**	**	**	*			***	***	*	**
	FLURAZEPAM 15mg.						FLURAZEPAM 30mg.				
13	55.3	36.0	36.5	29.0	48.2	19	73.3	158.5	44.2	17.5	18.5
14	30.5	21.0	25.2	39.5	35.8	20	93.7	11.5	19.8	118.5	81.3
15	23.7	6.5	5.1	13.5	10.8	21	48.8	21.0	21.6	22.0	31.2
16	37.8	38.0	44.1	29.0	24.5	22	70.2	62.0	70.2	39.5	56.2
17	.3	.0	1.1	2.0	1.8	23	44.3	11.5	11.8	23.5	28.2
18	43.5	41.5	21.8	27.0	18.0	24	22.3	8.5	11.3	35.5	38.3
MN	31.9	23.8	22.3	23.3	23.2		58.8	45.5	29.8	42.8	41.7
P(diff. from BSL)		**	*	NS	NS			NS	**	NS	NS

P(difference between QUAZEPAM change from BSL. and FLURAZEPAM change from BSL.)
(The BSL MEAN entries represent P(diff. between Q BSL and F BSL))

	BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN		BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN
15mg	NS	*	NS	NS	NS	30mg	*	NS	NS	NS	NS

Within treatment differences assessed by matched pair t-test, one tailed for baseline vs drug, two tailed for baseline vs post drug. Across treatment difference assessed by two tailed, non-paired t-test.

KEY:

NS	Not Significant at 0.10 level
*	Probability < 0.10
**	Probability < 0.05
***	Probability < 0.01

TABLE # 2
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QUAZEPAM STUDY 3

POLYGRAPHIC EFFICACY VARIABLE - ACROSS ALL SUBJECTS

LATENCY (MINUTES) TO PERSISTENT SLEEP ONSET

S#	BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN	S#	BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN
	QUAZEPAM 15mg.						QUAZEPAM 30mg.				
1	21.8	3.0	2.8	5.0	5.0	7	96.2	29.0	10.4	6.0	8.0
2	17.8	12.5	7.0	3.5	4.8	8	20.7	5.5	7.0	2.5	1.8
3	67.0	69.0	121.4	41.5	29.0	9	67.5	30.0	38.8	20.5	32.2
4	30.3	26.5	33.7	47.5	35.5	10	43.8	6.5	6.8	3.5	9.8
5	18.8	56.5	19.8	3.0	5.0	11	88.0	65.5	61.4	49.5	35.3
6	12.8	11.5	6.7	9.5	7.8	12	12.2	7.5	4.9	4.5	5.0
MN	28.1	29.8	31.9	18.3	14.5		54.7	24.0	21.6	14.4	15.4
P(diff. from BSL)		NS	NS	NS	*			***	**	**	**
S#						S#					
	FLURAZEPAM 15mg.						FLURAZEPAM 30mg.				
13	13.7	18.0	14.6	13.5	15.0	19	41.2	15.0	7.8	12.5	7.2
14	59.8	25.5	24.9	25.0	42.0	20	26.8	10.5	9.0	39.0	26.8
15	23.8	33.5	25.3	13.0	11.0	21	77.8	73.0	62.5	70.5	55.0
16	38.0	12.0	12.6	12.5	10.2	22	18.8	29.0	24.4	25.5	23.2
17	46.3	11.0	21.3	19.5	21.0	23	47.5	59.5	64.7	13.0	17.2
18	29.8	19.5	14.3	57.0	51.2	24	59.5	38.5	32.8	37.5	52.8
MN	35.2	19.9	18.8	23.4	25.1		45.3	37.6	33.5	33.0	30.4
P(diff. from BSL)		*	**	NS	NS			NS	*	NS	*

P(difference between QUAZEPAM change from BSL. and FLURAZEPAM change from BSL.)
(The BSL MEAN entries represent P(diff. between Q BSL and F BSL))

	BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN		BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN
15mg	NS	NS	NS	NS	NS	30mg	NS	*	NS	*	*

Within treatment differences assessed by matched pair t-test, one tailed for baseline vs drug, two tailed for baseline vs post drug. Across treatment difference assessed by two tailed, non-paired t-test.

KEY:

NS	Not Significant at 0.10 level
*	Probability < 0.10
**	Probability < 0.05
***	Probability < 0.01

TABLE # 2
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QUAZEPAM STUDY 3

POLYGRAPHIC EFFICACY VARIABLE - ACROSS ALL SUBJECTS

NUMBER OF AWAKENINGS

S#	BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN
	QUAZEPAM 15mg.				
1	26.7	22.0	14.8	10.0	10.5
2	7.7	5.0	5.0	5.0	6.0
3	9.0	4.0	5.0	5.0	4.5
4	16.0	6.0	7.2	17.0	13.5
5	10.3	17.0	11.0	2.0	8.0
6	9.0	9.0	9.8	18.0	11.0
MN	13.1	10.5	8.8	9.5	8.9
P(diff. from BSL)		NS	**	NS	NS
	FLURAZEPAM 15mg.				
13	11.0	10.0	10.0	8.0	7.5
14	18.3	14.0	16.4	24.0	23.5
15	15.7	9.0	4.0	16.0	11.0
16	11.7	12.0	16.6	12.0	11.0
17	2.0	1.0	1.4	3.0	5.0
18	17.3	20.0	14.6	12.0	12.0
MN	12.7	11.0	10.5	12.5	11.7
P(diff. from BSL)		NS	NS	NS	NS

S#	BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN
	QUAZEPAM 30mg.				
7	5.3	7.0	3.8	5.0	5.0
8	15.0	2.0	5.8	6.0	7.0
9	7.3	4.0	7.4	10.0	10.0
10	19.3	3.0	3.4	6.0	8.5
11	8.7	6.0	2.8	6.0	6.5
12	30.7	3.0	8.0	2.0	5.5
	14.4	4.2	5.2	5.8	7.1
		**	**	NS	NS
	FLURAZEPAM 30mg.				
19	12.3	35.0	16.2	15.0	12.5
20	17.0	1.0	3.4	9.0	10.5
21	23.3	18.0	17.6	16.0	16.5
22	14.3	8.0	9.2	11.0	9.0
23	10.0	4.0	5.8	6.0	9.0
24	14.0	9.0	9.2	9.0	17.5
	15.2	12.5	10.2	11.0	12.5
		NS	**	**	NS

P(difference between QUAZEPAM change from BSL. and FLURAZEPAM change from BSL.)
(The BSL MEAN entries represent P(diff. between Q BSL and F BSL))

	BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN
15mg	NS	NS	NS	NS	NS
30mg	NS	NS	NS	NS	NS

Within treatment differences assessed by matched pair t-test, one tailed for baseline vs drug, two tailed for baseline vs post drug. Across treatment difference assessed by two tailed, non-paired t-test.

KEY:

NS Not Significant at 0.10 level
* Probability < 0.10
** Probability < 0.05
*** Probability < 0.01

Efficacy:

Q15: On the first drug night, Q15 did not shorten sleep latency, but it did increase TST. On the mean drug night, Q15 did not shorten sleep latency or increase TST, but did decrease the number of awakenings, decreased wake time after sleep onset, and decreased wake time in last third of night.

Compared with baseline values, on the first post-drug night and on the mean post-drug night, TST increased, TWT decreased, wake time in the last third of the night decreased, and wake time after persistent sleep onset decreased. Thus, there was no evidence of a rebound insomnia but positive evidence for a hypnotic carryover effect.

Q30: On the first drug night as well as on the mean drug night, Q30 significantly improved all efficacy variables; sleep latency was shortened and TST increased. All indicators of sleep maintenance were improved; TWT and wake time in each third of the night were decreased, as well as the number of awakenings.

During the post-drug period, Q30 did not produce rebound insomnia but a hypnotic carryover effect was evident.

Safety:

Other than the possibility of some daytime drowsiness during withdrawal, no adverse effects were observed. Clinical lab tests included CBC, urinalysis, SMA-12 and EKG.

Comments:

Within treatment, analysis indicated that Q30 decreased sleep latency, increased sleep time, and improved sleep maintenance. After 5 nights of continuous administration, Q15 and Q30 produced a post-drug hypnotic carryover effect, and no rebound insomnia.

Some paradoxical results noted between quazepam and flurazepam at the 15mg and 30mg doses may be due to the small sample in each treatment group (n=6/group).

Objective: To assess and compare hypnotic effects of 30 mg quazepam and 0.5 mg triazolam on the sleep of chronic insomniacs who were otherwise free of medical or major psychological problems.

Experimental Design:

Parallel group design in which treatment was administered for 14 nights to 12 subjects (8 men and 4 women), who ranged in age from 32 to 55 yrs, with chronic insomnia. Subjectively, each subject took at least 45 minutes to fall asleep and slept less than 6 hours. On EEG-sleep recordings, on any two consecutive nights during nights 2-4, each subject had to sleep no more than 390 minutes during the 450 min recording period.

Schedule as follows:

Night 1: placebo (adaptation)
Night 2-4: placebo (baseline)
Night 5-18: drug (either quazepam 30 mg or triazolam 0.5 mg)
(Nights 5-7, in sleep lab; 8-14, at home; 15, readaptation; 16-18, intermediate effects)
Night 19-25: placebo (withdrawal)

Measurements:

1. TST (minutes)
2. Sleep efficiency (%): ratio of TST to total time in bed
3. Sleep latency (minutes): sleep induction time measured from "lights out" to first minute or more of stage 2 sleep
4. Total nocturnal wake time (minutes)
5. Duration of wakefulness and number of awakenings of 5 min or more in each third of night

Results: (refer to following tables in Volume 1.40)

I (p.18)
II (p.19)
III (p.20)
VI (p.23)

Average TST for Q30 baseline period was 347.59 minutes. During the first three nights (short term), Q30 increased it to 363.09 min and to 392.51 minutes during nights 16-18 (intermediate term). After 14 nights on Q30 and upon abrupt withdrawal, TST declined to 383.83 min on night 19 (Table VI) and to 361.22 min on night 20. On night 25, TST was 341.94 min, near baseline average.

Triazolam 0.5 mg increased TST from a baseline average of 363.33 min to 415.55 min on night 5. The average for nights 5-7 (short term) was 406.16 min, but decreased to 399.35 min for nights 16-18 (intermediate term). On the first withdrawal night 19, TST rapidly decreased to 213.39 min, and gradually reached baseline average of 368.89 min on night 25 (Table VI).

Upon comparing efficacy of Q30 and T 0.5mg, increase in TST from baseline for quazepam was 12.92% vs 9.91% for triazolam. On the first withdrawal night 19, increase in TST for quazepam was 10.42%; it decreased by 41.26% for triazolam (Table III).

At baseline, sleep latency for quazepam was 41.37 minutes and decreased to 31.77 minutes on the first night of administration and decreased further to 28.7 minutes (nights 5-7) and 25.16 minutes (nights 16-18). Thus, hypnotic efficacy increased progressively. In contrast, triazolam decreased sleep latency from baseline 32.56 min to 22.27 min, maintained it at 24.4 min, and slightly increased it to 27.18 minutes; and, on the first withdrawal night (night 19) it increased to 85.06 minutes demonstrating rebound insomnia (Table III).

When comparing efficacy of the two drugs tested, Q decreased nocturnal wakefulness from baseline by 44.75% after 2 weeks administration and by 35.69% on the first withdrawal night. Triazolam decreased it by 45.01% after 2 weeks and increased nocturnal wakefulness by 190.67% on the first withdrawal night (night 19 - Table III).

The short and intermediate-term (2 weeks) effects of 15 mg quazepam were examined on the sleep of 6 chronic insomniacs. Each subject was studied for 22 consecutive nights (4 baseline; 14 drug; 4 placebo withdrawal). The following data were obtained:

1. Sleep induction time (sleep latency): time from "lights out" until stage 2 sleep
2. TST
3. Sleep efficiency: ratio of TST to total time in bed
4. No of awakenings of 10 sec or more
5. Duration of wakefulness and number of awakenings of 10 sec or more in each third of the night

Results:

TST increased progressively on the first 3 nights of quazepam administration from 416.8 min to 429.2 to 432.7 minutes (Table III). Following drug withdrawal, TST returned to baseline values without any evidence for rebound insomnia.

In this study, 15 mg quazepam did not decrease sleep latency; however, the pre-treatment average sleep latency was only 27. minutes. Nevertheless, there was a significant decrease in wakefulness during the first third of the night.

There was poor correlation between the subjective and objective data.

three nights of its administration, this decrease did not reach statistical significance. After 2 weeks on quazepam the sleep latency was 28.8 minutes and on withdrawal it remained at about this level, 25.1 minutes. Quazepam, however, was active in the first third of the night. It significantly decreased the total period of wakefulness during the first third of the night immediately after it was started, from an average of 30.4 minutes during the baseline period to 17.8 minutes on nights 5, 6, and 7. Again, tolerance developed to this effect so that at the end of the two weeks of drug administration, the total period of wakefulness during the first third of the night on nights 15, 16 and 17 was 26.1

Table III — *Total sleep time on individual study nights*

Night	Total Sleep Time (min)	
	Mean	S.D.
1	385.6	45.4
2	413.7	26.9
3.	385.0	44.9
4	372.0	34.9
5	418.8	26.9
6	429.2	12.1
7	432.7	19.3
Home Nights 8-14		
15	409.2	46.4
16	420.3	34.1
17	400.6	37.1
18	422.3	18.7
19	395.2	39.1
20	390.2	42.3
21	417.2	30.0
22	383.7	41.4

minutes — a value not significantly different from baseline. During the second third of the night, quazepam significantly decreased the duration of wakefulness throughout the period of its administration, and an even greater decrease in the duration of wakefulness was observed in the third third of the night, but here, because of the great variability of the data, the decrease did not reach statistical significance. During the withdrawal period, the duration of wakefulness returned to baseline values in all three thirds of the night. In spite of the decrease in the total duration of wakefulness during the night, the number of awakenings of 10 seconds or more in duration each night was not significantly changed by 15 mg. of quazepam.

Quazepam produced significant differences in the duration and percentages of the different stages of NREM sleep (Table II). There was a progressive decrease in the duration and percentage of stage 1 sleep during the two-week drug administration period which persisted throughout the drug-withdrawal period. The duration and percentage of stage 2 sleep in contrast, rose progressively during the 2-week drug administra-

Objective: to evaluate effects of 15 mg and 30 mg quazepam (Q) and 30 mg flurazepam (F) on 17 insomniacs (22-60 yrs), administered drug for 28 consecutive nights, followed by a 15-night withdrawal period.

Study Design: 17 subjects were assigned to one of 3 drug groups in a double-blind manner:

Q 15 mg -- 5 subjects
Q 30 mg -- 6 subjects
F 30 mg -- 6 subjects

Schedule was as follows:

Nights 1-4:	on placebo (in sleep lab)
Nights 5-7:	active drug (in sleep lab)
Nights 8-14:	active drug (at home)
Night 15:	active drug (readaptation lab)
Nights 16-18:	active drug (in sleep lab)
Nights 19-28:	active drug (at home)
Night 29:	active drug (readaptation lab)
Nights 30-32:	active drug (in sleep lab)
Nights 33-47:	on placebo (withdrawal effects in lab)

Results:

Q 30 mg (Table 3): TWT decreased by 57.4% from 70.7 minutes (baseline) to 30.1 minutes (nights 5-7). On nights 16-18, TWT decreased from baseline by 30.3% to 49.3 minutes. On nights 30-32, TWT decreased from baseline by 22.6% to 54.7 minutes. Following drug withdrawal (nights 33-35), TWT remained below baseline, 49.3 minutes vs. 70.7 minutes.

F 30 mg (Table 4): TWT decreased by 51.1% from 100.6 minutes (baseline) to 49.2 min (nights 5-7). On nights 16-18, TWT decreased from baseline by 42.7% to 57.6 min. On nights 30-32, TWT decreased from baseline by 35.1% to 65.3 min. Following withdrawal (nights 45-47), TWT approximated baseline values, 103.3 min vs. 100.6 min.

Quazepam 15 mg (Table 5): TWT decreased by 37.5% from 95.2 min (baseline) to 59.5 min (nights 5-7). On nights 16-18, TWT decreased from baseline by 41.8% to 55.4 min. On nights 30-32, TWT decreased from baseline by 29.6% to 67.0 min. Following withdrawal (nights 33-35), TWT remained below baseline, 71.9 min vs. 95.2 min.

TABLE 3

Effectiveness of Quazepam 30 mg for Sleep Induction and Maintenance: Short-, Intermediate- and Long-term Drug Administration

	BSLN 2-4	DRUG 5-7	DRUG 16-18	DRUG 30-32	WDWL 33-35	WDWL 45-47
Sleep latency (min)	35.9	18.7	29.5	34.9	27.3	37.2
Wake time after sleep onset (min)	34.8	11.4†	19.8	19.8	22.0	21.9
Total wake time (min)	70.7	30.1†	49.3	54.7	49.3	59.1
Total no. of wakes	13.4	8.5†	11.4	11.6	11.5	10.2*
Per cent sleep time	85.3	93.7†	89.7	88.6	89.7	87.7
Per cent wake time by thirds of night						
1st	8.9	1.4†	3.0*	1.2†	1[illegible]	1.9†
2nd	4.4	2.1	4.8	3.9	7.6	6.0
3rd	10.5	3.7	5.1	7.9	5.3	6.7

All numbers represent mean values for the 6 subjects.

† $p<0.01$
* $p<0.05$

TABLE 4

Effectiveness of Flurazepam 30 mg for Sleep Induction and Maintenance: Short-, Intermediate- and Long-term Drug Administration

	BSLN 2-4	DRUG 5-7	DRUG 16-18	DRUG 30-32	WDWL 33-35	WDWL 45-47
Sleep latency (min)	55.7	31.1†	28.8†	40.9	42.7	63.6
Wake time after sleep onset (min)	44.9	18.1†	28.8	24.4*	44.7	39.7
Total wake time (min)	100.6	49.2†	57.6†	65.3*	87.4	103.3
Total no. of wakes	15.4	12.7	16.2	16.2	17.1	15.4
Per cent sleep time	79.0	89.7†	88.0†	86.4*	81.8	78.5
Per cent wake time by thirds of night						
1st	8.3	1.9	4.7	3.3	8.9	8.4
2nd	9.4	5.1	4.7	4.3	10.6	5.9
3rd	14.7	5.2	9.8	8.8	11.7	14.6

All numbers represent mean values for the 6 subjects.

† $p<0.01$
* $p<0.05$

TABLE 5

Effectiveness of Quazepam 15 mg for Sleep Induction and Maintenance: Short-, Intermediate- and Long-term Drug Administration

	BSLN 2-4	DRUG 5-7	DRUG 16-18	DRUG 30-32	WDWL 33-35	WDWL 45-47
Sleep latency (min)	57.3	37.3	27.0†	39.1	44.5	53.7
Wake time after sleep onset (min)	37.9	22.2	28.4	27.9	27.4	23.6
Total wake time (min)	95.2	59.5†	55.4†	67.0*	71.9	77.3
Total no. of wakes	14.7	11.5	12.9	13.1	13.8	12.5
Per cent sleep time	80.2	87.6†	88.5†	86.0*	85.0	83.9
Per cent wake time by thirds of night						
1st	4.9	2.9	2.4	1.5*	1.5*	1.7*
2nd	11.3	3.2	4.0	8.0	5.6	4.5
3rd	10.2	8.6	11.9	8.8	11.1	9.6

All numbers represent mean values for the 5 subjects.

† $p<0.01$
* $p<0.05$

These studies
may be regarded as pivotal to establishing that quazepam 30 mg significantly improved all efficacy variables: sleep latency was shortened and TST increased; TWT and wake time in each third of the night were decreased, as well as the number of awakenings. However, in both and studies, quazepam 15 mg did not shorten sleep latency, but did increase TST. In Kales' study, on baseline nights (2-4), sleep latency was 57.3 minutes. It decreased to 37.3 minutes after quazepam 15 mg (nights 5-7); with intermediate-term administration of Q 15 mg (nights 16-18), sleep latency was 27.0 minutes ($p < 0.01$). On nights 30-32 (long-term administration), sleep latency was 39.9 minutes.

There was no indication of rebound insomnia during the 15-day withdrawal period.

B. Short-term (5 night) Clinical Efficacy Studies of Quazepam (Q) 30 mg

Objective: to assess the safety and efficacy of 30 mg quazepam vs. placebo in out-patient insomniacs, as determined by daily, subjective self-evaluations by the patients and overall evaluations by patients and by investigators.

Design: balanced-parallel-groups; double-blind, placebo-controlled, randomized. For the first 3 nights, patients took placebo under single-blind conditions; for the last 5 nights, patients took either Q 30 mg or placebo.

Measurements: Efficacy was evaluated using responses on post-sleep questionnaires, and the physicians' and patients' global evaluations at the end of the study. Safety was evaluated using items 6, 7, and 8 on the daily post-sleep questionnaire and ADR, ECG and lab tests pre- and post-treatment.

Results:

Four U.S. investigators used a common protocol
) involving 176 outpatients.
was terminated after 6 months "because the investigator had only 14 valid cases (5 on Q30 and 9 on placebo)" and was unable to fulfill the protocol requirement of 60 cases.

In) involving 58 outpatients (29 on Q30 and 29 on placebo), no significant treatment differences in favor of Q30 were observed.

a total of 50 outpatients (25 on Q30 and 26 on placebo) were evaluated for efficacy and 57 patients (28 on Q and 29 on P) were evaluated for safety. Responses for the 6 efficacy items from the daily sleep questionnaire are summarized in Table 3. The results during the treatment period were significant on 3 or 4 nights, and consistently favored Q over placebo.

There was less morning alertness in the Q group (Table).

The most frequently reported ADR was daytime somnolence (16/28 on Q30 vs. 4/29 on placebo). Two patients (#44, #54) discontinued quazepam on the last study night due to ADR (somnolence) and one patient (#12) took only 15 mg Q on the last study night due to drowsiness the previous night.

. a total of 56 patients were evaluated (28 on Q and 28 on placebo). Four patients dropped out after the second night of treatment: two were Q-treated patients (#27, #56). Adverse reactions reported by #27 (daytime somnolence) and by #56 (daytime somnolence, hypokinesia and difficulty concentrating).

In the placebo group, patient #7 dropped out because of "treatment failure" and #31 reported daytime somnolence and nausea.

Responses for items 1 to 5 and item 9 on the post-sleep questionnaire, are tabulated on Table 4. Q30 induced sleep more quickly than placebo, and maintained sleep longer with fewer awakenings.

22 patients reported AR: 13 in the Q group and 9 in the placebo group. AR attributed to treatment are shown in Table 5. Daytime somnolence was reported most frequently: 12/28 in the Q-treated group and 5/28 in the placebo group.

Using the same protocol,
at the . 47 patients were evaluated for efficacy (24 on Q30 and 23 on placebo). One Q-treated patient (#25) dropped out because of severe daytime somnolence. Two placebo-treated patients dropped out: #3 because of a death in the family and #9 because of treatment failure. 15 patients reported AR (13 in Q group and 2 in placebo group). 10/24 on Q30 reported daytime somnolence and only 1/23 on placebo (See Table 6).

The responses for the 6 efficacy items from the daily sleep questionnaire are summarized in Table 4. Q30 was shown to be superior to placebo with respect to nocturnal awakenings, but not as regards to sleep latency or TST.

TABLE 1

SHORT TERM CLINICAL STUDY OF SCH 14134 IN OUTPATIENTS WITH INSOMNIA
STUDY NUMBER
SUMMARY OF RESULTS FOR THE PATIENT'S SLEEP QUESTIONNIRE
EFFICACY EVALUATIONS

		STUDY NIGHTS								
		BASELINE			DOUBLE-BLIND TREATMENT					OVERALL TREATMENT
QUESTION(NO.)	N*	1	2	3	4	5	6	7	8	4-8
SLEEP INDUCTION TIME(1)										
QUAZEPAM	24	2.9	3.1	3.1	4.0	4.2	3.8	4.1	3.9	4.0
PLACEBO	26	3.0	2.0	3.1	2.0	3.2	2.9	2.0	3.0	3.0
P-VALUE		NS	<.05	NS	.01	<.05	<.10	.01	.05	<.01
TOTAL SLEEP TIME(2)										
QUAZEPAM	24	2.0	2.5	2.2	1.3	3.5	3.4	3.6	3.4	3.4
PLACEBO	26	2.4	1.0	2.2	2.3	2.0	2.3	2.4	2.0	2.6
P-VALUE		NS	<.05	NS	<.05	NS	<.05	<.05	NS	<.01
NOCTURNAL AWAKENINGS(3)										
QUAZEPAM	24	1.0	1.2	1.2	3.0	3.7	3.6	4.0	3.5	3.7
PLACEBO	26	2.0	2.7	2.0	3.0	3.1	2.7	3.2	3.2	3.0
P-VALUE		NS	<.10	NS	<.05	.05	<.01	<.05	NS	<.01
EARLY MORNING AWAKEN.(4)										
QUAZEPAM	24	0.4	0.3	0.4	0.0	0.0	0.7	0.9	0.0	0.0
PLACEBO	26	0.6	0.2	0.1	0.4	0.7	0.6	0.5	0.5	0.5
P-VALUE		<.10	NS	NS	<.01	NS	NS	<.01	<.05	<.01
SLEEP QUALITY(5)										
QUAZEPAM	24	2.6	2.0	2.0	3.7	3.0	3.7	4.1	3.5	3.0
PLACEBO	26	3.0	2.4	2.0	3.0	3.3	2.9	3.2	3.2	3.1
P-VALUE		NS	<.10	NS	<.05	<.10	<.05	<.05	NS	.01
PATIENT RATING(9)										
QUAZEPAM	24	1.4	1.0	1.5	2.5	2.6	2.7	2.7	2.3	2.6
PLACEBO	26	2.0	1.4	1.0	1.0	2.2	2.0	2.1	2.1	2.0
P-VALUE		<.05	NS	NS	<.05	NS	<.05	<.05	NS	<.05

NS = NOT SIGNIFICANT (P>.10).
HIGHER SCORE INDICATES BETTER RESPONSE.

TABLE 4

SHORT TERM CLINICAL STUDY OF SCH 16134 IN OUTPATIENTS WITH INSOMNIA
STUDY NUMBER
SUMMARY OF RESULTS FOR THE PATIENT'S SLEEP QUESTIONNIRE
SAFETY EVALUATIONS

		STUDY NIGHTS								
		BASELINE			DOUBLE-BLIND TREATMENT					OVERALL TREATMENT
QUESTION(NO.)	N*	1	2	3	4	5	6	7	8	4-8
EASE OF AWAKENING(6)										
QUAZEPAM	24	3.1	3.3	3.0	3.1	2.8	2.7	2.3	2.7	2.7
PLACEBO	26	3.1	3.1	3.0	3.0	3.2	3.0	2.8	2.8	3.0
P-VALUE		NS	NS	NS	NS	NS	NS	<.10	NS	NS
MORNING ALERTNESS(7)										
QUAZEPAM	24	2.6	2.8	2.6	2.9	2.5	2.4	2.2	2.4	2.5
PLACEBO	26	3.0	2.9	2.9	3.0	3.2	3.0	3.1	3.0	3.1
P-VALUE		<.10	NS	NS	NS	.01	<.05	<.01	<.05	<.01
NIGHTMARES(8)										
QUAZEPAM	24	0.7	0.9	1.0	0.9	0.9	1.0	1.0	0.9	0.9
PLACEBO	26	0.9	0.7	0.9	0.8	0.9	0.9	0.9	0.9	0.9
P-VALUE		NS	NS	NS	NS	NS	NS	NS	NS	NS

NS = NOT SIGNIFICANT(P>.10).
HIGHER SCORE INDICATES BETTER RESPONSE.

TABLE 4

SHORT TERM CLINICAL STUDY OF SCH 16134 IN OUTPATIENTS WITH INSOMNIA
STUDY NO.

Summary of Results for the Patient's Sleep Questionnaire

Safety Evaluations

Question (No.)		N*	Study Nights: Baseline 1	2	3	Double-Blind Treatment 4	5	6	7	8	Overall Treatment 4-8
Ease of Awakening	(6)										
Quazepam		30	3.1	3.0	3.1	2.6	3.0	2.9	2.9	2.9	2.8
Placebo		30	3.1	3.0	2.9	3.0	2.9	3.1	3.1	2.9	2.9
P-Value			NS	NS	NS	<.10	NS	NS	NS	NS	NS
Morning Alertness	(7)										
Quazepam		30	2.8	2.8	2.8	2.8	2.9	2.9	2.8	2.9	2.8
Placebo		30	2.7	2.8	3.0	2.8	2.7	3.0	3.1	2.9	2.9
P-Value			NS	NS	NS	NS	NS	NS	NS	NS	NS
Nightmares	(8)										
Quazepam		30	0.8	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Placebo		30	1.0	1.0	1.0	0.9	0.9	0.9	0.9	0.9	0.9
P-Value			NS	NS	NS	NS	NS	NS	NS	NS	NS

* Refer to Table A2 (Appendix) for patients who missed answering one or more questions on any of the nights in the study.
NS = Not Significant (p>.10).
Higher score indicates better response.

Table 8. Number of Patients in Each Treatment Group Reporting Those Adverse Experiences Attributed to Treatment by the Project Physician

Adverse Experience	Number of Patients*	
	Quazepam	Placebo
Daytime somnolence†	10	1
Coordination abnormal	3	0
Dizziness	2	0
Headache	1	0
Mouth dry	0	1
Nausea	2	0
Tremor	1	0
Blurred vision	1	0

* Some patients reported more than one adverse experience.
† Probability of no difference between the groups: P<.01.

Table 4. Mean Values for Items 1 to 5 and Item 9 on the Patients' Postsleep Questionnaires for All Eight Study Nights and for the Overall Treatment Period.*

	Baseline Nights			Treatment Nights					
	1	2	3	4	5	6	7	8	Overall
Sleep Induction Time†									
Quazepam	3.2	3.0	3.0	3.4	3.8	4.0	3.7	3.9	3.7
Placebo	2.7	3.1	3.0	3.1	3.2	3.4	3.5	3.3	3.3
"p"	NSD	NSD	NSD	NSD	<.10	<.10	NSD	NSD	NSD
Total Sleep Time§									
Quazepam	2.0	2.6	2.8	3.2	3.5	3	3.8	3.2	3.4
Placebo	2.3	2.5	2.7	2.7	2.8	3.1	2.5	2.7	2.8
"p"	NSD	NSD	NSD	NSD	NSD	NSD	<.01	NSD	<.05
Nocturnal Awakenings¶									
Quazepam	2.9	3.2	3.4	4.3	4.4	4.4	4.3	4.3	4.3
Placebo	2.6	2.9	3.2	2.0	3.2	3.4	3.0	3.1	3.2
"p"	NSD	NSD	NSD	<.01	<.01	<.01	<.01	<.01	<.01
Early Morning Awakening#									
Quazepam	0.3	0.5	0.7	0.8	0.8	0.9	1.0	0.8	0.8
Placebo	0.5	0.5	0.7	0.7	0.8	0.6	0.6	0.6	0.7
"p"	<.10	NSD	NSD	NSD	NSD	<.10	<.01	<.10	<.05
Sleep Quality††									
Quazepam	2.8	2.9	3.3	3.9	4.0	4.0	4.1	3.9	4.0
Placebo	2.5	3.0	3.4	3.3	3.5	3.3	3.3	3.2	3.4
"p"	NSD	NSD	NSD	<.10	<.10	<.05	<.05	.05	<.01
Rating of Medication¶¶									
Quazepam	1.7	1.7	1.9	2.7	2.9	2.8	2.9	3.0	2.9
Placebo	1.6	1.7	2.1	2.0	2.3	2.2	2.2	2.3	2.2
"p"	NSD	NSD	NSD	<.05	<.05	.05	<.05	<.05	<.01

* "p" is the probability of no difference between the groups. NSD = no significant difference.

† Rated on a scale of 1 to 5: 5 = 0 to 15 min, 4 = 16 to 30 min, 3 = 31 to 45 min, 2 = 46 to 60 min, 1 = >60 min.

§ Rated on a scale of 1 to 5: 5 = >8 hr, 4 = 7.1 to 8 hr, 3 = 6.1 to 7 hr, 2 = 5.1 to 6 hr, 1 = 5 hr or less.

¶ Rated on a scale of 1 to 5: 5 = no awakenings, 4 = 1, 3 = 2 or 3, 2 = 4 or 5, 1 = 6 or more.

Rated on a scale of 0 or 1: 1 = no, 0 = yes.

†† Rated on a scale of 1 to 5: 5 = excellent, 4 = good, 3 = fair, 2 = poor, 1 = no sleep.

¶¶ Rated on a scale of 1 to 4: 4 = excellent, 3 = good, 2 = fair, 1 = poor.

C. Short-term (5 night) Clinical Efficacy Studies of Quazepam (Q15) vs Placebo

Objective: to assess safety and efficacy of 15 mg quazepam (Q) vs placebo in out-patient insomniacs, as determined by daily patient sleep questionnaires and the investigator's global evaluation at the end of the study.

Design: randomized, double-blind, parallel-groups, consisting of a 3-night single-blind placebo baseline phase and a 5-night double-blind treatment phase.

Measurements: Responses for items 1 to 5 were scored on an increasing scale with highest numbers always indicating most favorable responses, i.e., better sleep. Safety was evaluated using items 6, 7, and 8 on the daily post-sleep questionnaires and the results of PE, ECG and lab tests.

Results:

Three investigators used a common protocol involving 155 outpatients. 's study was terminated after 14 months because only 37 patients had been empaneled and the investigator could not complete the study in a reasonable length of time. No statistically significant results were obtained on the efficacy measures.

, differences between Q15 and placebo on TST were not statistically significant. Q15 induced sleep more quickly than placebo and there were fewer nocturnal awakenings. (Table 4).

Patients in quazepam group dropped out because of treatment failure, and patient on placebo.

differences between Q15 and placebo were not significant in regards to TST and sleep latency. Significant differences in favor of Q15 were observed in 3/4 nights with respect to nocturnal awakenings (Table 4). Daytime somnolence was reported by 7 patients on Q15 and 4 on placebo ($p > .20$).

Two additional investigators used the same short-term protocol comparing Q15 vs placebo (In c's there were no statistically significant differences between Q15 and placebo in regards to efficacy. Patient reported mild nervousness.

Table 3. Mean Values for Items 1 to 5 and Item 9 on the Patients' Postsleep Questionnaires for All Eight Study Nights and for the Overall Treatment Period.*

	Baseline Nights			Treatment Nights					
	1	2	3	4	5	6	7	8	Overall
Sleep Induction Time†									
Quazepam	2.8	3.2	3.4	3.7	3.6	3.5	3.9	3.8	3.7
Placebo	3.3	3.4	3.6	3.7	3.8	3.8	3.2	3.6	3.6
"p"	NSD	NSD	NSD	NSD	NSD	NSD	.10	NSD	NSD
Total Sleep Time§									
Quazepam	2.1	1.9	2.0	3.1	3.0	3.0	3.1	3.0	3.0
Placebo	2.4	2.3	2.6	2.7	2.9	2.9	2.6	2.7	2.8
"p"	NSD	NSD	<.10	NSD	NSD	NSD	NSD	NSD	NSD
Nocturnal Awakenings¶									
Quazepam	3.2	3.2	3.4	4.0	3.9	3.8	4.0	4.1	4.0
Placebo	2.8	2.8	3.2	3.2	3.4	3.6	3.2	3.3	3.4
"p"	NSD	NSD	NSD	<.01	<.10	NSD	<.01	<.01	<.01
Early Morning Awakening#									
Quazepam	0.4	0.4	0.4	0.6	0.7	0.8	0.8	0.8	0.8
Placebo	0.5	0.6	0.5	0.6	0.5	0.7	0.6	0.5	0.6
"p"	NSD	<.10	NSD	NSD	NSD	NSD	<.05	<.01	<.05
Sleep Quality**									
Quazepam	2.7	2.6	2.8	3.6	3.5	3.8	3.8	3.7	3.7
Placebo	2.6	2.7	3.1	3.1	3.1	3.2	3.0	2.8	3.0
"p"	NSD	NSD	NSD	.05	NSD	<.01	<.01	<.01	<.01
Rating of Medication††									
Quazepam	1.7	1.6	1.7	2.6	2.6	2.7	2.8	2.7	2.7
Placebo	1.8	1.8	1.9	2.0	2.2	2.3	2.0	2.0	2.1
"p"	NSD	NSD	NSD	.01	NSD	<.05	<.01	<.01	<.01

* "p" is the probability of no difference between the groups. NSD = no significant difference.

† Rated on a scale of 1 to 5: 5 = 0 to 15 min, 4 = 16 to 30 min, 3 = 31 to 45 min, 2 = 46 to 60 min, 1 = >60 min.

§ Rated on a scale of 1 to 5: 5 = >8 hr, 4 = 7.1 to 8 hr, 3 = 6.1 to 7 hr, 2 = 5.1 to 6 hr, 1 = 5 hr or less.

¶ Rated on a scale of 1 to 5: 5 = no awakenings, 4 = 1, 3 = 2 or 3, 2 = 4 or 5, 1 = 6 or more.

Rated on a scale of 0 or 1: 1 = no, 0 = yes.

** Rated on a scale of 1 to 5: 5 = excellent, 4 = good, 3 = fair, 2 = poor, 1 = no sleep.

†† Rated on a scale of 1 to 4: 4 = excellent, 3 = good, 2 = fair, 1 = poor.

Table 4. Mean Values for Items 1 to 5 and Item 9 on the Patients' Postsleep Questionnaires for All Eight Study Nights and for the Overall Treatment Period.*

	Baseline Nights			Treatment Nights					
	1	2	3	4	5	6	7	8	Overall
Sleep Induction Time†									
Quazepam	2.6	2.9	3.1	3.7	3.5	3.7	3.9	3.7	3.7
Placebo	2.6	2.7	2.8	2.8	2.9	2.9	3.0	3.0	2.9
"p"	NSD	NSD	NSD	<.05	NSD	<.05	<.10	<.10	<.05
Total Sleep Time§									
Quazepam	2.2	2.4	2.8	3.2	3.2	3.3	3.3	3.1	3.2
Placebo	2.3	2.2	2.5	2.7	2.5	2.8	2.8	2.8	2.7
"p"	NSD	NSD	NSD	NSD	<.05	NSD	NSD	NSD	<.05
Nocturnal Awakenings¶									
Quazepam	3.2	3.2	3.4	3.8	3.7	3.9	3.9	3.6	3.8
Placebo	3.1	3.1	3.3	3.4	3.3	3.3	3.4	3.4	3.4
"p"	NSD	NSD	NSD	<.10	<.10	<.05	NSD	NSD	<.05
Early Morning Awakening#									
Quazepam	0.7	0.6	0.6	0.7	0.7	0.7	0.6	0.6	0.7
Placebo	0.5	0.4	0.4	0.6	0.6	0.5	0.6	0.7	0.6
"p"	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD
Sleep Quality**									
Quazepam	2.8	2.9	3.2	3.8	3.7	3.7	3.9	3.4	3.7
Placebo	3.1	2.9	3.1	3.2	3.1	3.3	3.5	3.3	3.3
"p"	NSD	NSD	NSD	.01	<.05	NSD	NSD	NSD	<.05
Rating of Medication††									
Quazepam	1.8	2.2	2.2	2.7	2.7	2.8	2.7	2.6	2.7
Placebo	2.1	1.8	2.1	2.2	2.2	2.1	2.3	2.4	2.2
"p"	NSD	NSD	NSD	<.05	<.05	.01	NSD	NSD	<.01

* "p" is the probability of no difference between the groups. NSD = no significant difference.

† Rated on a scale of 1 to 5: 5 = 0 to 15 min, 4 = 16 to 30 min, 3 = 31 to 45 min, 2 = 46 to 60 min, 1 = >60 min.

§ Rated on a scale of 1 to 5: 5 = >^ hr, 4 = 7.1 to 8 hr, 3 = 6.1 to 7 hr, 2 = 5.1 to 6 hr, 1 = 5 hr or less.

¶ Rated on a scale of 1 to 5: 5 = no awakenings, 4 = 1, 3 = 2 or 3, 2 = 4 or 5, 1 = 6 or more.

Rated on a scale of 0 or 1: 1 = no, 0 = yes.

** Rated on a scale of 1 to 5: 5 = excellent, 4 = good, 3 = fair, 2 = poor, 1 = no sleep.

†† Rated on a scale of 1 to 4: 4 = excellent, 3 = good, 2 = fair, 1 = poor.

, there were no significant differences between Q15 and placebo, with the exception of a marginal difference for TST on the fifth night ($p < .10$). Whereas 7 patients on Q15 reported daytime somnolence, only one did on placebo ($p = .02$). Patient reported abnormal coordination, and patient reported dizziness.

Two short-term studies in inpatients, comparing Q 15 mg vs placebo were carried out under protocol:

did an 8-night (3 nights, single-blind; 5 nights, double-blind), parallel-group study in 56 in-patients withdrawing from chronic alcoholism. The results were not statistically signficant for any of the effecacy items on the 56 patients' sleep questionnaire (Table 2). The patients showed less morning alertness in the Q15 group compared to the placebo group ($p = .05$) (Table 3). Patient on Q15 reported dry mouth and patient #35, a rash on placebo.

Only hospitalized patients entered
This study was terminated prematurely because
was unable to enroll the required number of patients in a reasonable length of time. Two patients on Q15 experienced AR: #1 was groggy and #3 was drowsy. Patient #2 on placebo had nightmares on study day 5.

D. Single-dose Studies in Presurgical Patients:

Four studies) were done comparing the efficacy and safety of Q 30 mg and 15 mg vs placebo, in hospitalized patients scheduled for elective surgery on the following day. Data were collected primarily from questionnaires and patient interviews.

Objective: to assess hypnotic activity and safety of 30 mg quazepam vs. placebo when administered at bedtime to hospitalized patients scheduled for elective surgery the next morning.

Design: double-blind parallel groups. The patients took either Q30 or placebo at 10:00 p.m. on the night before elective surgery. Patient could request remedication (with safe and effective hypnotic), if not asleep within 2 hrs. In the morning, before any pre-op medications, the investigator administered a patient questionnaire.

Table 2. Mean Values for Items 1 to 5 and Item 9 on the Patients' Postsleep Questionnaires for All Eight Study Nights and for the Overall Treatment Period.*

	Baseline Nights			Treatment Nights					
	1	2	3	4	5	6	7	9	Overall
Sleep Induction Time†									
Quazepam	3.1	3.1	3.2	3.3	3.5	3.2	3.5	3.7	3.4
Placebo	3.1	3.2	3.2	3.6	3.7	3.7	3.7	3.8	3.7
"p"	NSD	NSD	NSD	NSD	NSD	<.10	NSD	NSD	NSD
Total Sleep Time§									
Quazepam	2.8	3.0	2.8	2.9	3.1	3.0	3.2	3.5	3.2
Placebo	2.6	2.9	2.9	3.0	3.2	3.1	3.2	3.2	3.1
"p"	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD
Nocturnal Awakenings¶									
Quazepam	3.6	3.8	3.8	3.6	3.7	3.7	3.8	3.8	3.7
Placebo	3.4	3.7	3.4	3.8	3.6	3.6	3.9	3.7	3.7
"p"	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD
Early Morning Awakening#									
Quazepam	0.7	0.8	0.8	0.3	0.8	0.8	0.8	0.9	0.9
Placebo	0.7	0.9	0.6	0.9	0.8	0.9	0.8	0.9	0.9
"p"	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD
Sleep Quality**									
Quazepam	3.5	3.7	3.7	3.6	3.8	3.6	3.7	3.7	3.7
Placebo	3.5	3.6	3.6	3.8	3.9	3.7	4.0	3.9	3.8
"p"	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD
Rating of Medication††									
Quazepam	2.7	2.6	2.8	2.6	2.9	2.6	2.8	2.8	2.7
Placebo	2.5	2.5	2.8	2.9	3.0	2.8	3.1	2.8	2.9
"p"	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD

* "P" is the probability of no difference between the groups. NSD = no significant difference.

† Rated on a scale of 1 to 5: 5 = 0 to 15 min, 4 = 16 to 30 min, 3 = 31 to 45 min, 2 = 46 to 60 min, 1 = >60 min.

§ Rated on a scale of 1 to 5: 5 = >8 hr, 4 = 7.1 to 8 hr, 3 = 6.1 to 7 hr, 2 = 5.1 to 6 hr, 1 = 5 hr or less.

¶ Rated on a scale of 1 to 5: 5 = no awakenings, 4 = 1, 3 = 2 or 3, 2 = 4 or 5, 1 = 6 or more.

Rated on a scale of 0 or 1: 1 = no, 0 = yes.

** Rated on a scale of 1 to 5: 5 = excellent, 4 = good, 3 = fair, 2 = poor, 1 = no sleep.

†† Rated on a scale of 1 to 4: 4 = excellent, 3 = good, 2 = fair, 1 = poor.

Table 3. Mean Values for Items 6, 7, and 8 on the Patients' Postsleep Questionnaires for All Eight Study Nights and for the Overall Treatment Period.*

	Baseline Nights			Treatment Nights					
	1	2	3	4	5	6	7	8	Overall
Ease of Awakening†									
Quazepam	3.0	3.0	2.8	2.7	2.7	2.7	2.7	2.7	2.7
Placebo	3.0	3.0	3.0	2.9	2.8	2.9	2.9	2.9	2.9
"p"	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD
Morning Alertness§									
Quazepam	2.9	2.8	2.9	2.6	2.7	2.7	2.8	2.7	2.7
Placebo	3.1	2.8	2.8	3.1	2.9	3.1	2.8	2.9	2.9
"p"	NSD	NSD	NSD	<.05	NSD	NSD	NSD	NSD	<.05
Nightmares¶									
Quazepam	1.0	0.9	1.0	1.0	1.0	1.0	1.0	0.9	1.0
Placebo	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
"p"	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD

* "P" is the probability of no difference between the groups. NSD = no significant difference.
† Rated on a scale of 1 to 4: 4 = very easily, 3 = easily, 2 = with difficulty, 1 = with much difficulty.
§ Rated on a scale of 1 to 4: 4 = wide awake and fully alert, 3 = alert but not at peak, 2 = a little drowsy, 1 = very drowsy.
¶ Rated on a scale of 0 or 1: 1 = no, 0 = yes.

Results:

, 31 patients received Q30, and 30 placebo. 2/31 on Q30 received remedication with a standard hypnotic, and 5 of the remaining 29 took longer than 2 hrs to fall asleep; therefore, treatment was considered a failure in these 7/31 patients on Q30. Treatment was rated a success for 23 patients on Q30. In the placebo group, 10/30 patients received remedication, 6 of the remaining 20 took longer than 2 hrs to fall asleep; treatment was considered a failure in 16/30 patients.

Among the 49 patients who were not remedicated (29 on Q30 and 20 on placebo), the difference in sleep induction time between the 2 groups was not statistically significant (p=.26).

, 33 patients received Q30 and 33 placebo. 13/33 on Q30 needed remedication with a standard hypnotic and were considered treatment failures. The remaining 20 patients fell asleep within 2 hrs and were considered successful. In the placebo group, 15/33 needed remedication and were considered failures. Of the remaining 18 patients, 7 took longer than 2 hrs to fall asleep and were also regarded as failures. Thus, the success rate of Q30 was higher than placebo (61% for Q30 vs 29% placebo).

Among the 38 patients who were not remedicated (20 on Q30 vs 18 placebo), those on quazepam fell asleep more quickly ($p < .01$).

), the same protocol is used, except that the patients are given quazepam 15 mg instead of 30 mg. 7/30 on Q15 needed remedication with a standard hypnotic and were considered as treatment failures. Of the remaining 23 patejnts, 6 took longer than 2 hrs to fall asleep, and were rated as failures. In the placebo group, 11/29 needed remedication and 6/18 took longer than 2 hrs to fall asleep; thus, 17 were regarded as failures. Treatment was successful for 55% on Q15 and 39% on placebo; the difference between the groups was not significant (p=.35).

In this single-dose study, 100 hospitalized patients received quazepam 15 mg, Q30, flunitrazepam 1 mg, F2mg, or placebo orally on the night before elective surgery. There were 20 patients in each group, whose data were evaluable for both efficacy and safety.

Flunitrazepam (Rohypnol) a long-acting (t1/2=10-20 hrs) hypnotic, is not marketed in the U.S. This is another benzodiazepine where there is accumulation of the drug during daily administration.

Comments: Quazepam 30 mg taken on the night before elective surgery by 64 hospitalized patients, was more effective than placebo. However, quazepam 15 mg taken by 30 patients did not achieve significant results.

E. Long-Term (12-week) Clinical Safety Studies:

Eight investigators conducted this 14-week (12 weeks double-blind treatment, followed by 2 weeks single-blind placebo) trial comparing the safety of quazepam 30 mg vs. flurazepam 30 mg, in outpatients with chronic insomnia. Data were collected by the following investigators and subsequently pooled.

Objective: multicentric study to evaluate safety of Q30 vs. flurazepam 30 mg during 12 weeks of treatment and to identify AR that might arise from inappropriate long-term use.

Design: double-blind, randomized, unbalanced-parallel-groups design, with two-thirds of patients receiving Q30. During weeks 1 to 12, patients took assigned treatment; placebo withdrawal in single-blind fashion during weeks 13 and 14 (see Table IV p. 14).

Visit 1: screening: history, PE, ophthalmologic, vital signs, 12-lead ECG, lab tests.
Visit 2: within 10 days for vital signs, brief neurological exam. Medication dispensed for first 2 weeks.
Visits 3,4,5,6 & 7: scheduled to return at end of weeks 2, 4, 8, 12, and 14.
ADR reported at visits 3 to 7, and prn by phone.
Lab tests: monthly at visits 4, 5 and 6.
Repeat eye exam and ECG at visit 6.

Table 1. Schedule of Events in Long-term Safety Study C79-041 With Eight Investigators.

	Visit 1 (Screen)	Visit 2 (Pretrial)	Visit 3 (Week 2)	Visit 4 (Week 4)	Visit 5 (Week 8)	Visit 6* (Week 12)	Visit 7 (Week 14)
Medical History	X	-	-	-	-	-	-
Physical Examination	X	-	-	-	-	X	X
Vital Signs	X	X	X	X	X	X	X
Ophthalmologic Examination	X	-	-	-	-	X	†
Brief Neurologic Examination	X	X	X	X	X	X	X
Electrocardiogram	X	-	-	-	-	X	†
Laboratory Tests	X	-	-	X	X	X	†
Adverse Experience Reports§	-	-	X	X	X	X	X
Acceptance of Treatment:							
Patient Rating	-	-	X	X	X	X	X
Investigator Rating	-	-	X	X	X	X	-
Dispense Medication:							
Active Treatment	-	X	X	X	X	-	-
Placebo	-	-	-	-	-	X	-

* Or any time that a patient discontinued treatment.

† Performed again if results at previous visit were different from results at screening visit in a clinically significant way.

§ Adverse experiences could also be reported any time between visits that was necessary.

Results:

381 patients were enrolled by 8 investigators (254 on Q30 and 127 on F30). No data exists for 12 patients (lost to follow-up). Thus, there were evaluable data for 369 patients (247 on Q and 122 on F). Table 2 shows the distribution of patients among the 8 investigators.

There were 137 men and 232 women; ages ranged form 18 to 86 yrs with a mean of 48 yrs. Demographic data for 369 patients are presented in Table 3. Table 4 presents insomnia characteristics. Table [illegible] (p. 59) presents distribution of patients by reason and time of dropout.

Table 17 presents the distribution of dropouts by individual investigators and the reason for dropping out (ADR or treatment failure). Seventy patients dropped out because of ADR, 52 (21%) in the quazepam group and 18 (14.7%) in the flurazepam group (p=.147).

Reported ADR:

Of the 247 patients who began treatment with quazepam, 111 (44.9%) dropped out; in the flurazepam group, 42 (34.4%) of the 122 dropped out (p=.054).

No. Patients Reporting Specific ADR During Treatment

	Quazepam (N=247)	Flurazepam (N=122)
Daytime somnolence	85 (34%)	41 (34%)
Hypokinesia	45 (18%)	21 (17%)
Ataxia	35 (14%)	11 (9%)
Confusion	18 (7%)	7 (6%)
Dizziness	14 (6%)	6 (5%)
Depression	13 (5%)	4 (3%)

The incidence of ADR did not differ significantly in the two treatment groups.

Clinically significant events occurred in the following patients:

a male patient (born 4/15/31), having a 20 yr history of asthma, died on 6/6/80. This patient entered the study on 5/5/80, and had completed 12 weeks of quazepam 30 mg. He died during an acute attack of asthma in the first week of placebo withdrawal (wk 13).

Table 2. Disposition of Patients by Investigator and by Treatment Group (Q=Quazepam and F=Flurazepam)

Number of Patients			
Empaneled*		Evaluated	
Q	F	Q	F
40	20	40	20
41	20	41	20
49	24	43	22
31	16	30	16
17	8	17	7
37	18	37	17
23	12	23	12
16	9	16	8
234	127	247	122
381		369	

Table 3. Summary of Demographic Data.*

	Treatment Group	
	Quazepam	Flurazepam
No. of Patients Treated	247	122
Age in Years		
<21	4	1
21 to 30	39	17
31 to 40	81	35
41 to 50	54	34
51 to 60	66	34
>60	3	1
Sex		
male	94	43
female	153	79
Race		
white	229	114
black	13	6
other	4	1
not specified	1	1

* There was no significant difference between the groups (P>.10).

Table 6. Distribution of Patients in Each Treatment Group by Insomnia Characteristics and History.*

	Quazepam	Flurazepam
Severity of Insomnia		
mild	4	0
moderate	115	50
severe	127	72
Type of Insomnia		
acute	6	2
sporadic	24	10
chronic	216	109
Duration of Insomnia		
1 year	67	38
>1 to 2 years	66	33
>2 to 5 years	41	19
>5 years	71	32
Number of Episodes per Week		
<4	25	11
5	40	17
6	31	17
7	150	76

* There was no significant difference between the groups (P>.10).

TABLE 3

A LONG-TERM CLINICAL STUDY OF SCH 16134 IN OUTPATIENTS WITH INSOMNIA

Distribution of Patients by Reason and Time of Dropout

Reason for Dropout	Treatment Group	Time in Weeks <2	>2-4	>4-8	>8-12	>12	Total
Adverse Reactions	Quazepam	21	8	14	5	0	48
	Flurazepam	8	5	3	1	0	17
Treatment Failure	Quazepam	1	2	3	2	2	10
	Flurazepam	0	3	0	0	1	4
Other	Quazepam	9	7	14	8	11	49
	Flurazepam	6	4	4	3	4	21
Total	Quazepam	31	17	31	15	13	107
	Flurazepam	14	12	7	4	5	42

Dropouts - Double-Blind Phase (30 mg Quazepam) 12-week study

Investigator	Q	F	Q	F	Q	F	Q	F	Q	F	Q	F	Q	F	Q	F
No. patients	40	20	41	20	45	22	30	16	17	7	37	17	23	12	16	8
Reason:																
Adverse reactions	10	2	16	4	5	5	8	1	2	2	4	1	5	1	2	--
Treatment failure	3	--	2	2	2	--	--	1	--	--	2	--	4	1	1	1
Other	1	--	5	2	14	8	9	3	6	2	3	2	5	3	2	1
Total	14	2	23	8	21	13	17	5	8	4	9	3	14	5	5	2

n	Quazepam 247	Flurazepam 122
Total Dropouts	111 44.9%	42 34.4%
Due to ADR	52 21%	18 14.7%

NDA 18-708
Quazepam

, a 59-yr old woman had visual hallucinations and severe ataxia, weakness, confusion and disorientation, dizziness, and daytime somnolence after 2 weeks on quazepam 30 mg (5/12-26, 1981). After stopping the medication, all her symptoms abated and no residual effects were noted.

Patient No. 5, a posterior subcapsular cataract (CD) was noted at the post-study ophthalmologic exam, after 12 weeks of quazepam 30 mg, in a 48-yr old male patient. A pre-study eye exam had been reported as normal. found no causal relationship to the medication taken (7/1/81).

Laboratory Tests:

Table // (Vol. 1.59; p. 32) summarizes the results for nine selected tests, including indicators of renal and hepatic function. For each test, the table shows mean pre-treatment and post-treatment values, and the number of patients whose post-treatment values increased or decreased from baseline, stratified by percentage ranges. The results were judged to be clinically signficant in 3 quazepam-treated patients and one flurazepam-treated patient; these results are briefly discussed in Table /2 (Vol. 1.59; p. 34).

a 46-yr old woman with no previous history of liver disease, had increases in SGOT and SGPT at weeks 4 and 8 of treatment with quazepam 30 mg. At the week 8 visit, the patient reported pain and fullness in the RUQ of the abdomen, but the liver was not palpable. Treatment was discontinued at this time. Levels of SGOT and SGPT, along with values for alkaline phosphatase (alk phos) and total bilirubin, are shown below (with normal ranges):

	SGOT (14-40)	SGPT 14-75)	alk phos (12-37)	Total Bili (0.4-1.4)
Screening	25	65	23	0.7
wk 4	52	89	24	0.5
wk 8	61	110	25	0.3
(follow-up)				
after 2 wks	47	38	16	0.4
after 4 wks	79	118	23	0.4
after 7 wks	46	76	22	0.4

states that the patient is well and reports no symptoms. He believes that the increase in SGOT and SGPT was related to quazepam administration, but did not rule out the possibility of another uspecified cause.

ECG and Vital Signs:

No clinically signficant change was observed in the ECG's and vital signs, including heart rate and BP.

Table 11. Summarization of Results From Nine Selected Laboratory Tests: Mean Values Before and After Treatment, and Percentage Changes From Baseline.

Laboratory Tests	Group	Sample Size	Mean Values		Number of Patients With Percent Changes			
			Baseline	After Treatment	Decreases of 25% to 100%	Changes Within 25%	Increases of 25% to 99%	Increases of ≥ 100%
Hemoglobin Level	Q	237	14.7	14.5	1	235	1	0
	F	122	14.5	14.3	0	122	0	0
Hematocrit	Q	237	43.3	42.9	1	236	0	0
	F	122	43.0	42.0	0	122	0	0
Total White Blood Cell Count	Q	237	7.4	7.2	25 (11%)	190 (80%)	22 (9%)	0
	F	122	7.4	7.3	8 (6%)	102 (84%)	11 (9%)	1 (1%)
Blood Urea Nitrogen (BUN)	Q	239	14.0	13.9	30 (13%)	170 (71%)	36 (15%)	3 (1%)
	F	122	14.0	13.9	14 (12%)	92 (75%)	15 (12%)	1 (1%)
Creatinine	Q	238	1.10	1.09	34 (14%)	179 (75%)	20 (9%)	5 (2%)
	F	122	0.99	1.03	15 (12%)	90 (74%)	14 (12%)	3 (2%)
Total Bilirubin	Q	238	0.56	0.50	57 (24%)	117 (49%)	55 (23%)	9 (4%)
	F	122	0.50	0.49	29 (24%)	66 (54%)	23 (19%)	4 (3%)
Alkaline Phosphatase	Q	238	51.7	51.5	19 (8%)	196 (82%)	19 (8%)	4 (2%)
	F	122	56.0	53.7	16 (13%)	96 (79%)	8 (6%)	2 (2%)
Serum Glutamic Oxaloacetic Transaminase (SGOT)	Q	238	20.8	22.5	49 (21%)	133 (56%)	43 (18%)	13 (5%)
	F	120	20.7	19.6	25 (21%)	75 (63%)	16 (13%)	4 (3%)
Serum Glutamic Pyruvic Transaminase (SGPT)	Q	237	22.2	26.8	54 (23%)	115 (49%)	51 (21%)	17 (7%)
	F	120	23.3	22.5	30 (25%)	60 (50%)	25 (21%)	5 (4%)

Table 12. Patients With Clinically Significant Increases from Baseline in Laboratory Tests.

Investigator	Patient	Laboratory Values	Comments
DIAZEPAM GROUP:			
	8 (48 yrs female)	SGOT (14-40) rose from 25 at baseline to 61 at week 4 and 79 at week 8 when treatment was discontinued. SGPT (14-75) rose from 65 to 89 to 110 at the same time. Total bilirubin and alkaline phosphatase were within normal limits.	Investigator and project physician attributed increase in SGOT and SGPT to treatment. See text for more details.
	11 (31 yrs male)	SGOT (5-21) rose from 23 at baseline to 396 at week 10; SGPT (2-28) rose from 16 to 848, and BUN (5-20) rose from 11 to 24 at the same time. Treatment was discontinued. Total bilirubin, alkaline phosphatase, and creatinine were within normal limits.	liver palpable and tender. Patient admitted self-administering intravenous drugs with nonsterile needle and syringe. Specialized laboratory tests indicated non A, non B type hepatitis. Patient recovered fully after treatment for hepatitis. Not attributed to treatment.
Brenner	4 (39 yrs male)	SGPT (4-25) rose from 35 at baseline to 128 at week 4 and was 108 at week 5 when treatment was discontinued. SGOT (5-26) also rose from 20 at baseline to 60 at week 4 and was 38 at week 5. Alkaline phosphatase (16-70) increased from 65 to 82 at week 4 and was 77 at week 5. Total bilirubin was within normal limits.	Patient has a history of alcoholism and admitted to drinking during the study. Abnormalities not attributed to treatment.
FLURAZEPAM GROUP:			
	19 (48 yrs female)	SGPT (0-46) rose from 26 at baseline to 154 two weeks after treatment was discontinued during week 3 (because of intercurrent illness). SGOT (0-41) increased from 35 to 56 and alkaline phosphatase (30-115) was up from 96 to 168. Total bilirubin was within normal limits.	Patient had been in hospital for two weeks for treatment of arthritis, and had received many unspecified concomitant medications. Abnormalities not attributed to treatment with study drug.

II. Stucies in Geriatric Patients - Quazepam 15 mg

A. Short-term (5 nights) Clinical Efficacy:

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a. Investigator:
(internist)

b. Subjects: 63/70 (7 cropped out during placebo baseline) were evaluated for safety (31 on Q, 32 on P). 57/63 (6 subjects had protocol deviations) were evaluated for efficacy (30 Q, 27P). Ages 60 or over; all subjects had at least 2 complaints (difficulty falling asleep, frequent awakenings, less than 6 hrs TST).

c. Results: for the overall treatment period, only TST, sleep quality, and patient rating of medication were statistically signficant ($p < .01$) in favor of Q15 ~~vs~~ over placebo.

---

a. Investigator:

b. Subjects: 60 (30 on Q, 30 on P); median age 69

c. Results: Q 15 mg induced sleep more quickly than placebo, maintained sleep longer and produced a better quality of sleep. Daytime somnolence was reported by 12-quazepam treated patients and by 3 on placebo.

---

a. Investigator:

b. Subjects: 60 (31 on Q, 29 on P); median age 71

c. Results: a high placebo response was evident in the patients' global evaluations; only one patient in the placebo group rated therapy poor.

Comments:

Of the 3 short-term (5 nights), double-blind, placebo-controlled studies, comparing the efficacy of quazepam 15 mg vs placebo, in geriatric insomniacs, only the stucy by) is acceptable; Q15 increased TST significantly better than placebo.

B. Long-term (14-nights) Clinical Safety of Quazepam 15 mg vs. F. regular 15 mg

a. Subjects: 101 patients were enrolled by the 3 investigators (51 on Q 15 mg, 50 on F 15 mg). There were 32 men and 69 women; ages ranged from 65-87 yrs.

b. Results: overall incidences of dropouts were not significantly different between the 2 groups ($p > .10$): 5/51 in quazepam group and 4/50 in flurazepam group. One quazepam and 3 flurazepam patients dropped out because of ADRs.

The number of patients reporting treatment related AR are shown in Tables 7 (p. 21) and 8 (p.23).

15 patients reported new AR during (1 wk) placebo withdrawal; 11/15 were recurrences of insomnia. Three quazepam patients reported nausea, anorexia and confusion. Abrupt discontinuation of quazepam was not associated with a withdrawal phenomenon.

Comments:

Three investigators studied 101 geriatric insomniacs in a randomized double-blind clinical trial. At the end of 2 weeks treatment, 73% (37/51) of quazepam patients and 84% (42/50) of flurazepam patients rated treatment as satisfactory ($p=.19$).

C. Effects of Treatment on Memory and Psychomotor Performance in Geriatric Insomniacs (in volume 1.67)

a. Subjects: 48 patients were enrolled by 3 investigators: 16 on Q 15 mg, 17 on F 15 mg, and 15 on placebo. Ages ranged from 64-86 yrs.

b. Results:

Efficacy: effects on sleep latency and ~~and~~ TST (EEG). Both Q15 and F15 were significantly superior to placebo ($p<.05$) with respect to improvement from baseline in TST on first night of treatment. None of the differences in sleep latency were significant.

Psychomotor performance evaluations were carried out at 8:30 a.m. and 4:30 p.m. on the days following each night spent in the sleep lab (screening and days 2, 3, 9 and 16) by means of the following:

Wilkinson Auditory Vigilance Test
4-part Card-Sorting Test
Digit-symbol substitution and copying test

As seen from Table 3 (p. 47) no consistent pattern was observed. In general, there was no deterioration in the quazepam group.

Safety: 23/46 reported one or more ADR: 11 in Q group, 6 in F group and 6 in placebo. Two patients in quazepam group discontinued drug because of ADR:

Patient : 84 yr old woman had severe ataxia and daytime somnolence after night 3.

Patient : 80 yr old man experienced ataxia, diplopia, abnormal coordination and somnolence.

The most frequently reported ADRs were somnolence, fatigue and ataxia. Reports of treatment-related ADR were significantly ($p < .05$) higher in the quazepam group (8/16) than in either of the other 2 groups (F=2/17; P=3/15).

Comments:

Three investigators ( ) conducted this 16-day (1 day placebo baseline, 7 days double-blind treatment, 7 days placebo washout) trial comparing the efficacy, safety and effects on psychomotor performance of Q 15 mg vs F 15 mg and placebo in 48 geriatric outpatients. Post-treatment observation revealed no evidence of withdrawal in any patient.

III. Special Studies:

Effects of Quazepam 15 mg and 30 mg and pentobarbital 50 mg and 150 mg vs placebo on CR function (in vol. 1.30) of healthy adults.

Investicator:

Design:

Single oral doses of quazepam 15 mg and 30 mg, pentobarbital 50 and 150 mg and placebo were administered to 5 healthy males, according to a randomized, DB, Latin square design. Each subject received each of the 5 treatments. One dose was given per week with at least 5-day "washout" intervals. The effects of each drug on respiratory function were measured at baseline and at 1/2, 1, 2, 3, and 4 hrs after drug administration, and on cardiac function at baseline and at 45, 75, and 135 minutes after drug administration.

Results: Quazepam 30 mg produced slight respiratory depression at 3 hrs.

There were no significant drug effects on the slope of the respiratory response curve. This study, in 5 healthy males, suggests that clinically the respiratory and CV effects of quazepam and pentobarbital, at the doses studied, are not significant.

C81-029-01: Secretion of quazepam in breast milk.

Comments:

This study has been reviewed in the detailed review by the Division of Biopharmaceutics (dated 4/26/83; pp 12 and 13). Four healthy, non-pregnant lactating females (26-32 yrs) completed this study. Each subject received a single oral 15 mg quazepam tablet. Breast milk and blood samples were analyzed by gas chromatographic methods, to determine levels of quazepam and its metabolites.

There is excretion of quazepam and its two major active metabolites into breast milk. Through 48 hours following single 15 mg dose administration, total excretion of quazepam, 2-oxoquazepam and N-desalkylflurazepam in breast milk was only 0.11% of the administered quazepam dose.

7788B

NDA 18-706 Quazepam

Overall Evaluation:

Quazepam is a hypnotic agent which is related to flurazepam. It is a 1,4-benzodiazepine derivative containing a trifluorethyl, sulfur, and aryl group in the first, second, and fifth positions, respectively (refer to structural formula).

Quazepam has an interesting metabolic and pharmacokinetic profile. Quazepam is rapidly and well absorbed with peak plasma levels reached at approximately 2 hours; 2-oxoquazepam (a major metabolite) was rapidly formed with peak plasma levels occurring at about 4 hours. Both compounds declined in comparable biphasic patterns, with elimination half-lives of approximately 40 hours.

Following oral administration of ^{14}C-quazepam in solution form, the drug is rapidly and extensively absorbed, distributed, metabolized and slowly excreted in the urine and feces over a 5-day period.

The two major active plasma metabolites are 2-oxoquazepam and N-desalkylflurazepam. The latter is quazepam's major metabolite at steady state and identical to that seen at steady state with flurazepam. In geriatric patients, the elimination half-life of N-desalkylflurazepam is about twice that of young adults (t1/2=73 hours).

The following studies can be regarded as adequate and well-controlled to support the claims for substantial evidence of relative safety and efficacy for quazepam 15 mg tablets.

A. Objective studies: sleep lab studies which are considered by this reviewer as furnishing substantial evidence of the efficacy of quazepam (15 mg) for short and intermediate-term use:

_____: On the first drug night, Q_{15} increased TST, and on the mean drug night Q_{15} decreased the number of awakenings, decreased wake time after sleep onset and decreased wake time in the last third of the night. On drug withdrawal, there was no evidence of a rebound insomnia.

_____: After Q_{15}, sleep latency decreased from 57.3 minutes to 37.3 minutes, and there was no indication of rebound insomniac during the 15-day withdrawal period.

B. Subjective Studies (until the 1960's, these traditional clinical trials were the only means of evaluating the safety and efficacy of hypnotic drugs.)

Short-term (5 night) quazepam 30 mg: in

. quazepam performed significantly ($p<.05$) better with respect to the efficacy parameters (sleep induction time, TST, nocturnal awakenings).

However, significantly more quazepam patients experienced daytime somnolence and less morning alertness than placebo patients.

Short-term (5 night), quazepam 15 mg: in

. differences between Q_{15} and placebo were not significant in regards to TST. Q_{15} induced sleep more quickly than placebo and there were fewer nocturnal awakenings. In general, Q_{15} did not perform as well (relative to placebo) as Q_{30} with respect to efficacy parameters.

However, Q_{15} showed fewer significant differences with respect to morning alertness and daytime somnolence than Q_{30}.

Short-term (5 night in geriatric patients:
quazepam 15 mg increased TST significantly better than placebo.

Other Studies:

Single-dose studies in presurgical patients:

quazepam 30 mg was administered on the night before elective surgery. These studies yielded consistent results in favor of quazepam 30 mg over placebo with respect to efficacy parameters. Similar favorable results were not achieved by quazepam 15 mg

Effect of Q15 and Q30 vs. placebo on CR function:
in 5 healthy males suggests that clinically, the respiratory and CV effects of Q_{15} are not significant; however, Q_{30} produced slight respiratory depression at 3 hours. Furthermore, patient a 49 year old male, having a 20 year history of asthma, died on 8/9/80. This patient had completed 12 weeks on Q_{30}. He died during an acute attack of asthma in the first week of placebo withdrawal (week 13). It should be noted that the carry-over effectiveness of Q_{30} after withdrawal may be ascribed to the long half-lives of the drug and its metabolites.

NDA 18-708 (Quazepam)

Dose-Ranging Studies:

The following two studies were conducted in the sleep lab by investigators with recognized expertise in the conduct of such studies.

This was a DB four-night parallel groups study of placebo vs. quazepam 15, 30, and 45 mg., preceeded by a four night single-blind adaptation and baseline period wherein everyone took placebo,

, and was followed by a two-night single-blind placebo withdrawal period.

24 Ss (17 women and 7 men; ages 31 to 62 years) with insomnia (minimum 3 month history of requiring at least 45 minutes to fall asleep and sleeping less than 6 1/2 hours per night) were studied. Six subjects were randomly assigned to each of 4 treatment groups on nights 5-8: placebo, Q_{15} mg, Q_{30}, and Q_{45} mg.

Sleep was assessed objectively by polysomnographic recordings. Sleep was also assessed subjectively by questionnaires completed by each S each lab morning.

Results:

TST (total sleep time): During the drug period (nights 5-8), TST was almost dose related. Placebo, 15 mg, 30 mg and 45 mg had 376, 400, 419 and 418 minutes sleep, respectively. During the postdrug period (nights 9-10), Q_{30} and Q_{45} had significantly longer sleep times compared with placebo. The higher the dose during the drug period, the longer the sleep during the postdrug period, and also the more the sleep on the first postdrug night.

Sleep latency: During the drug period (nights 5-8), sleep latency was shorter in the Q_{45} ($p<0.05$) and in the Q_{30} ($p<0.08$) than in the placebo group. Also sleep latency was shorter during the drug period than during baseline in Q_{45} ($p<0.01$) and in the Q_{30} ($p=0.05$). Compared to baseline sleep latency, postdrug sleep latency was less in both Q_{45} ($p<0.01$) and Q_{30} ($p=0.05$). Q's effect on sleep latency was not significant at the 15 mg dose.

Nocturnal awakenings: During the drug period (nights 5-8), Q_{30} and Q_{45} significantly reduced the number of nocturnal awakenings; Q_{15} also reduced nocturnal number of awakenings, but not significantly.

Over the four nights (5-8) all three doses of quazepam significantly increased subjective sleep time. During this period, compared with placebo, each Q treated group had significantly shorter subjective sleep latency, and better subjective sleep quality.

Witndrawal effects: In the Q_{30} and Q_{45} groups, the sleep time increase and sleep latency decrease of the drug period persisted during the postdrug nights. This finding suggests that like flurazepam, when Q was administered for several consecutive nights, Q or an active metabolite accumulated in the recipient.

There were no clinically significant differences in the pre and post study PE, EKG's, CBC, SMA-12 or urine tests. Two subjects (#10 and #14) who received Q_{45} mg reported exressive sleepiness each morning following all four nights of drug administration.

Although Q_{15} mg reduction of insomnia was less than at the higher doses (Q_{30} and Q_{45}) the Q_{15} mg dose may be preferable in that there is less likelihood of a dose-related psychomotor performance deficit.

Quazepam was evaluated in doses of 7.5, 15, and 30 mg in a 12-night protocol including four nights of drug trial.

18 insomniacs (more than 45 min. to fall asleep and/or less 5 hrs. TST), ages 22-58 years, were selected from the Sleep Disorders Clinic. Ss were assigned to one of 3 dose groups (6S/group) in a DB fashion.

Results:

Effectiveness of $Q_{7.5}$, Q_{15}, Q_{30} for sleep induction and maintenance

Quazepam	Baseline nights 2-4	Drug nights 5-8	Withdrawal 9-12
7.5 mg			
Sleep latency (min)	39.6	26.8**	23.1**
Wake time after sleep onset	27.1	13.4	29.6
Total wake time	66.7	40.2**	57.7
Total no. of wakes	13.0	10.5	12.0
15 mg			
Sleep latency (min)	38.4	25.5	34.6
Wake time after sleep onset	34.8	13.6**	31.0
Total wake time	73.2	39.2*	65.7
Total no. of wakes	13.2	09.1	12.1
30 mg			
Sleep latency (min)	44.0	27.9*	19.4*
Wake time after sleep onset	39.4	12.5*	19.1*
Total wake time	83.4	40.5*	38.5*
Total no. of wakes	14.9	10.5*	11.6*

all numbers represent mean values for the 6 Ss
* $p < 0.01$
** $p < 0.05$

Quazepam's effects during both drug use and withdrawal appeared to be dose related: 15 mg induced a greater reduction in wake time after sleep onset than the 7.5 mg dose, and 30 mg induced even greater differences in both wake time after sleep onset and total wake time.

At each dose level, subjective reports of improvement in sleep latency and TST were in agreement with the objective data on quazepam's effectiveness.

Side effects appeared to be dose-related in terms of severity. None of the subjects in the 7.5 mg group reported symptoms of "hangover". In the 15 mg group, 3 Ss (#11, 15R, 17) reported feeling "tired" in the morning after the first drug night, while one subject (#9) had symptoms of moderate morning hangover for the first two mornings after drug administration. In the 30 mg group, moderate morning hangover was evident in 2 Ss following the last three nights of drug administration and into the first withdrawal night (#3 and #13).

Conclusions:

1. On 4/18/84, the sponsor informed us that they had re-evaluated NDA 18-708 and had decided to market only the 15 mg dosage. In a dose-response study considered 7.5 and 15 mg as the optimal doses for quazepam. Although Q_{15} did not perform as well (relative to placebo) as the 30 mg dose with respect to the efficacy parameters, there was less morning hangover and daytime sleepiness.

2. The absence of a placebo treatment group, in the long-term (12-week) clinical safety study did not permit a proper assessment of the long-term safety of quazepam 30 mg.

3. Quazepam is contraindicated in patients with COPD, and in patients with established or suspected sleep apnea.

4. During the 15 nights after abrupt withdrawal of quazepam administered for 28 consecutive nights, there was no rebound insomnia (i.e., a marked or statistically significant worsening of sleep above baseline levels). This would be expected in a drug with long half-lives of elimination. In 1973, hypothesized that when bensodiazepines with a long half-life are withdrawn, effects on the BZ receptors are less abrupt because the endogenous BZ-like compounds may be partially restored before the active metabolites of the exogenously administered drugs are completely eliminated.

5. In the short-term (5 nights) study in geriatric insomniacs, Q_{15} increased TST significantly better than placebo. In the long-term (14 nights) studies, abrupt discontinuation of Q_{15} was not associated with a withdrawal phenomenon, during the third week.

6. In the 7-nights study in geriatric insomniacs, at no time was there a significant deterioration in psychomotor performance or memory while on Q_{15}. Post-treatment observation for a week revealed no evidence of withdrawal in any patient.

7. In spite of the shortcomings inherent in sleep lab studies from the limited number of subjects and the high cost per subject night, the more rigorous control of experimental variables contributes to a more precise evaluation of hypnotic drug efficacy than is obtainable with general clinical trials.

Recommendations:

1. NDA 18-708 for quazepam 15 mg tablets is approvable for the following indication:

   "As a hypnotic for the short term treatment of insomnia characterized by difficulty in falling asleep and/or maintaining sleep." For transient insomnia related to minor situational stress (e.g., hospitalization for elective surgery), a benzodiazepine with a short half-life is preferable.

2. Labeling needs to be revised.

3. SBA to follow.

T. T. Woo, M.D.

Theresa T. Woo, M. D.
(Medical Officer, HFN-120)

cc:
~~Orig: NDA 18-708~~
HFN-120 T Hayes 06-03-85
HFN-220
HFN-120/TTWoo/1/8/85
ft/mb/1/8/85
DOC 3008a

Table I - Parameters of nocturnal sleep and wakefulness

		Baseline 2-3-4		Short Term 5-6-7		Intermediate Term 16-17-18		Immediate Withdrawal 20-21-22		Long Term Withdrawal 23-24-25	
		X	S.D.	X	S.D.	X	S.D.	X	S.D.	X	S.D.
1. Total Recording Time (min)	Q	450.00		450.00		450.00		450.00		450.00	
	T	450.00		450.00		450.00		450.00		450.00	
2. Total Sleep Time (min)	Q	347.59	32.42	283.09	69.87	392.51*	43.26	370.20	61.66	369.81	48.28
	T	363.33	22.60	406.16*	16.72	399.35*	6.73	393.48*	26.09	377.09+□	27.65
3. Sleep Efficiency (%)	Q	77.28	7.24	85.15	15.54	87.22*	9.61	82.33	13.73	83.97*▲	11.41
	T	80.75	5.03	90.26*	3.72	88.76*	1.51	85.77	7.76	83.80+	6.15
4. Sleep Latency (min)	Q	41.37	19.53	28.70*	18.67	25.48	17.93	20.24*	12.94	18.45*+	9.68
	T	32.96	38.43	24.40	15.08	27.18	5.87	17.00▲	8.47	20.31	10.53
5. Total Nocturnal Wakefulness (min)	Q	95.40	37.17	62.31	70.13	52.70*	42.36	74.63	62.54	70.50▲	48.92
	T	80.90	21.03	36.63*	14.94	44.48*	8.35	50.81*	23.61	67.61+□	25.91
6. Wakefulness during 1st 3rd of night (min)	Q	44.18	17.03	27.27*	16.12	25.50*	16.62	18.22*+	13.23	22.03*	9.57
	T	35.85	31.71	21.38	11.39	27.14	3.32	17.64▲	4.99	21.61	7.77
7. Wakefulness during 2nd 3rd of night (min)	Q	21.38	18.28	7.55	11.33	7.33*	7.40	8.83	6.84	10.83	9.44
	T	12.96	10.16	3.13	2.52	2.48	1.70	8.44	10.52	12.57+▲	8.79
8. Wakefulness during 3rd 3rd of night (min)	Q	32.61	18.02	27.48	45.70	21.87	25.07	47.57▲	46.73	35.14	36.86
	T	31.81	19.67	12.11*	9.70	14.85	8.43	24.72	16.37	33.70+	20.75
9. # of awakenings during the night	Q	3.06	0.98	0.72*	0.53	0.83*	0.46	1.22*	0.75	1.39*	1.16
	T	2.11	1.03	0.78*	0.72	0.89*	1.00	1.50	0.86	1.50	0.55

Legend: Average values and standard deviations of the variables listed above are given for each of the 5 assessment periods. Statistical comparisons were done between all 5 assessment periods.
* indicates that the average value is significantly different from the baseline line average ($p<0.05$)
+ indicates that the average value is significantly different from the average of the short term treatment period ($p<0.05$)
▲ indicates that the average value is significantly different from the average of the intermediate term treatment period ($p<0.05$)
□ indicates that the average value is significantly different from the average of the immediate withdrawal period ($p<0.05$).

Table II - Parameters of nocturnal sleep and wakefulness

		Baseline 2-3-4 X	S.D.	Night 5 X	S.D.	Night 19 X	S.D.	Night 25 X	S.D.
1. Total Recording Time (min)	Q	450.00		450.00		450.00		450.00	
	T	450.00		450.00		450.00		450.00	
2. Total Sleep Time (min)	Q	347.59	32.42	377.16	68.53	383.83▽	73.04	341.94	83.18
	T	363.33	22.60	415.55	10.51	213.39	87.29	368.89	24.99
3. Sleep Efficiency (%)	Q	77.28	7.24	83.84	14.36	85.29▽	16.23	81.36	19.40
	T	80.75	5.03	92.34	2.33	47.41	19.40	81.97	5.56
4. Sleep Latency (min)	Q	41.37	19.63	31.77	21.17	27.39	31.25	15.65	11.95
	T	32.96	38.43	22.27▽	17.22	85.00	66.50	17.38	9.06
5. Total Nocturnal Wakefulness (min)	Q	95.40	37.17	68.50	65.33	61.16	73.52	87.27	81.93
	T	80.90	21.03	26.50	10.01	235.16▽	88.27	75.83	24.23
6. Wakefulness during 1st 3rd of night (min)	Q	44.18	17.03	35.61	20.51	25.16	31.17	18.83	9.69
	T	35.85	31.71	15.83	11.04	96.16▽	37.09	24.39	15.40
7. Wakefulness during 2nd 3rd of night (min)	Q	21.38	18.28	4.38	2.87	4.61	5.16	16.89	22.92
	T	12.96	10.16	1.61	1.47	58.05	58.48	5.77	6.43
8. Wakefulness during 3rd 3rd of night (min)	Q	32.61	18.02	28.50	49.57	31.38	41.98	44.11	59.08
	T	31.81	19.67	9.05	6.80	80.94	47.27	45.66	34.21
9. # of awakenings during the night	Q	3.06	0.98	1.33	1.03	1.17	0.75	1.00	1.10
	T	2.11	1.03	0.67	0.82	3.33	3.08	1.17	0.75

Legend: For the variables listed above, average values and standard deviations are given for the baseline period and nights 5, 19 and 25 individually. Statistical comparisons for the same night were done between the two drugs tested.
▽ indicates that the average value is significantly different ($p<0.05$) from the average value of the other drug, when compared for the same night.

Table III - Parameters of nocturnal sleep and wakefulness

		Baseline 2-3-4	Intermediate Term 16-17-18		Night 19	
		X	X	Efficacy from baseline	X	Efficacy from baseline
1. Total Sleep Time (min)	Q	347.59	392.51*	+12.92%	383.83▽	+ 10.42%
	T	363.33	399.35*	+ 9.91%	213.39	- 41.26%
2. Sleep Efficiency (%)	Q	77.28	87.22*	+12.86%	85.29▽	+ 10.36%
	T	80.75	88.76*	+ 9.91%	47.41	- 41.28%
3. Sleep Latency (min)	Q	41.37	25.48	-38.40%	27.39	- 33.87%
	T	32.96	27.18	-17.53%	85.00	+157.88%
4. Total Nocturnal Wakefulness (min)	Q	95.40	52.70*	-44.75%	61.16	- 35.89%
	T	80.90	44.48*	-45.01%	235.16▽	+190.67%

Legend:

* indicates that the average value is significantly different from the baseline average ($p < 0.05$)
▽ indicates that the average value is significantly different ($p < 0.05$) from the average value of the other drug, when compared for the same night.

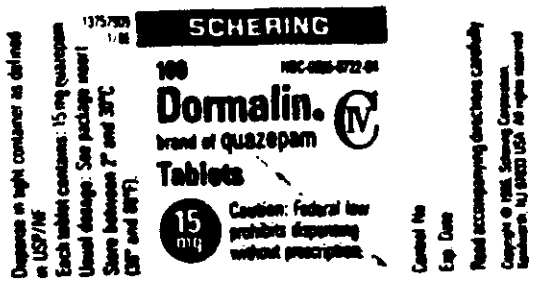
Table VI - Total sleep time on individual study nights

Night			Total Sleep Time (minutes) Quazepam $\bar{X}$	S.D.	Triazolam $\bar{X}$	S.D.
1	PLACEBO		324.38	69.45	359.89	28.77
2			339.22	55.03	367.00	29.51
3			344.99	32.74	356.72	32.13
4			358.55	43.27	366.27	38.48
5			377.16	64.53	415.55	10.51
6			394.94	43.31	398.50	24.47
7			377.16	104.52	404.44	20.85
Home Nights	8 - 14					
15			363.33	80.83	386.44	19.01
16			398.38	44.35	400.27	10.88
17			389.50	50.82	398.05	18.02
18			389.67	47.38	399.72	13.28
19	DRUG		383.83▽	73.04	213.39	87.29
20			361.22	72.81	395.22	19.31
21			380.00	48.41	407.67	22.32
22			369.39	82.34	377.55	58.70
23			380.44	51.34	379.16	52.19
24			387.05	52.67	383.22	52.93
25			341.94	83.18	368.89	24.99

Legend:

▽ Indicates that the average value is significantly different ($p<0.05$) from the average value of the other drug when compared for the same night.

DORMALIN Tablets, 15 mg
Label for 100



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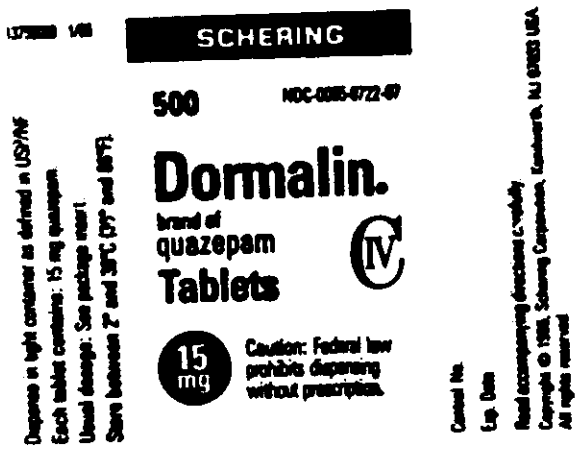
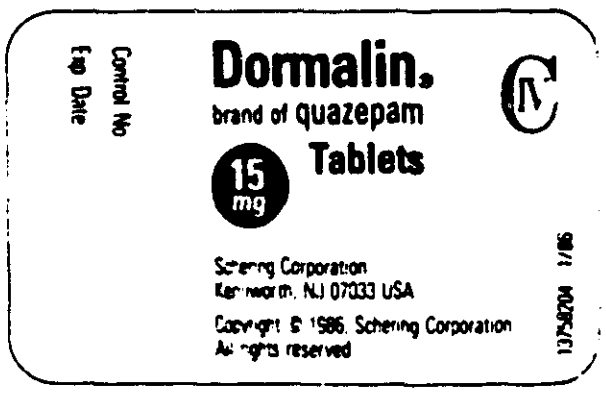
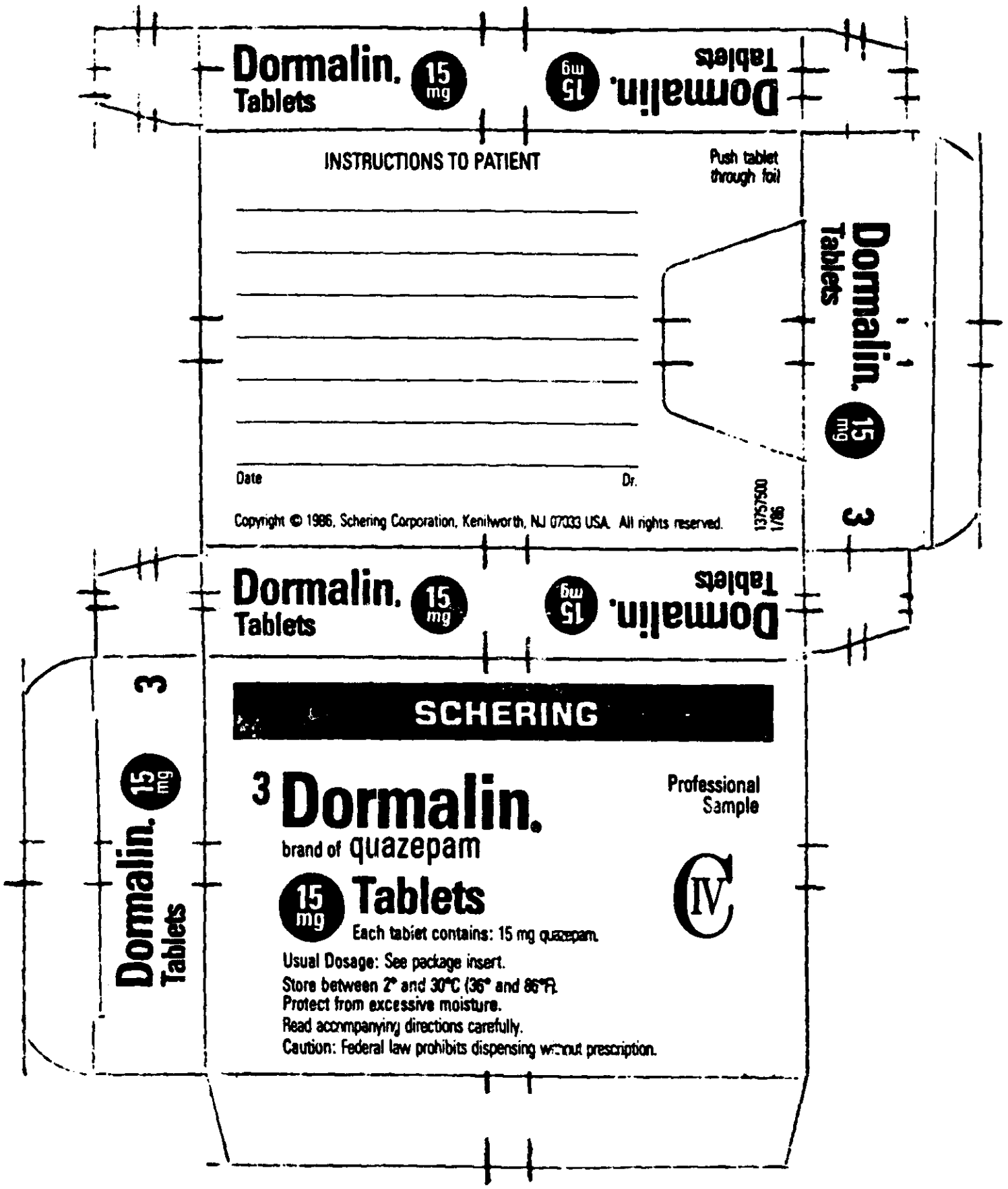


MADE IN JAPAN

DORMALIN Tablets
Backing



DORMALIN Tablets
Carton for 3, professional sample



5

Carcinogenesis, Mutagenesis, Impairment of Fertility Quazepam showed no evidence of carcinogenicity or other significant pathology in oral oncogenicity studies in mice and hamsters.

Quazepam was tested for mutagenicity using the L5178Y TK+/-Mouse Lymphoma Mutagenesis Assay and Ames Test. The L5178Y TK+/-Assay was equivocal and the Ames Test did not show mutagenic activity.

Reproduction studies in mice conducted with quazepam at doses equal to 60 and 180 times the human dose of 15 mg, and with diazepam at 67 times the human dose, produced slight reductions in the pregnancy rate. Similar reduction in pregnancy rates have been reported in mice dosed with other benzodiazepines, and is believed to be related to the sedative effects of these drugs at high doses.

Teratogenic Effects: Pregnancy Category X (See **CONTRAINDICATIONS, Usage in Pregnancy** section.) *Reproduction studies* of quazepam in mice at doses up to 400 times the human dose revealed no major drug-related malformations. Minor developmental variations that occurred were delayed ossification of the sternum, vertebrae, distal phalanges and supraoccipital bones, at doses of 66 and 400 times the human dose. Studies with diazepam at 200 times the human dose showed a similar or greater incidence than quazepam. A reproduction study of quazepam in New Zealand rabbits at doses up to 134 times the human dose demonstrated no effect on fetal morphology or development of offspring.

Nonteratogenic Effects The child born of a mother who is taking benzodiazepines may be at some risk of withdrawal symptoms from the drug during the postnatal period. Neonatal flaccidity has been reported in children born of mothers who had been receiving benzodiazepines.

Labor and Delivery DORMALIN Tablets have no established use in labor or delivery.

Nursing Mothers Quazepam and its metabolites are excreted in the milk of lactating women. Therefore, administration of DORMALIN Tablets to nursing women is not recommended.

Pediatric Use Safety and effectiveness in children below the age of 18 years have not been established.

ADVERSE REACTIONS Adverse events most frequently encountered in patients treated with quazepam are drowsiness and headache.

Accurate estimates of the incidence of adverse events associated with the use of any drug are difficult to obtain. Estimates are influenced by drug dose, detection technique, setting, physician judgments, etc. Consequently, the table below is presented solely to indicate the relative frequency of adverse events reported in representative controlled clinical studies conducted to evaluate the safety and efficacy of quazepam. The figures cited cannot be used to predict precisely the incidence of such events in the course of usual medical practice. These figures also cannot be compared with those obtained from other clinical studies involving related drug products and placebo.

The figures cited below are estimates of untoward clinical event incidences of 1% or greater among subjects who participated in the relatively short duration placebo-controlled clinical trials of quazepam.

	DORMALIN (15 mg)	PLACEBO
NUMBER OF PATIENTS TREATED	267	268
% OF PATIENTS REPORTING		
Central Nervous System		
Daytime Drowsiness	12.0%	3.3%
Headache	4.5%	2.2%
Fatigue	1.9%	0
Dizziness	1.5%	<1%
Autonomic Nervous System		
Dry Mouth	1.5%	<1%
Gastrointestinal System		
Dyspepsia	1.1%	<1%

The following incidences of laboratory abnormalities occurred at a rate of 1% or greater in patients receiving quazepam and the corresponding placebo group. None of these changes were considered to be of physiological significance.

	DORMALIN		PLACEBO	
NUMBER OF PATIENTS	234		244	
% of Patients Reporting	Low	High	Low	High
Hematology				
Hemoglobin	1.4	0	1.2	0
Hematocrit	1.5	0	1.7	0
Lymphocyte	1.3	1.6	1.2	1.9
Eosinophil	*	1.5	*	1.3
SEG	1.1	*	1.6	*
Monocyte	*	1.1	*	*
Blood Chemistry				
Glucose	*	*	*	1.2
SGOT	*	1.3	*	1.1
Urinalysis				
Specific Gravity	*	*	*	1.1
WBC	0	2.6	0	3.0
RBC	0	*	0	1.1
Epithelial Cells	0	2.5	0	3.2
Crystals	0	*	0	1.0

*These laboratory abnormalities occurred in less than 1% of patients. In addition, abnormalities in the following laboratory tests were observed in less than 1% of the patients evaluated: WBC count, platelet count, total protein, albumin, BUN, creatinine, total bilirubin, alkaline phosphatase, and SGPT.

The following additional events occurred among individuals receiving quazepam at doses equivalent to or greater than those recommended during its clinical testing and development. There is no way to establish whether or not the administration of DORMALIN caused these events.

Hypokinesia, ataxia, confusion, incoordination, hypertunesia, speech disorder, and tremor were reported.

Also, depression, nervousness, agitation, amnesia, anorexia, anxiety, apathy, euphoria, impotence, decreased libido, paranoid reaction, nightmares, abnormal thinking, abnormal taste perception, abnormal vision, and cataract were reported.

Also reported were urinary incontinence, palpitations, nausea, constipation, diarrhea, abdominal pain, pruritus, rash, asthenia, and malaise.

The following list provides an overview of adverse experiences that have been reported and are considered to be reasonably related to the administration of benzodiazepines: incontinence, slurred speech, urinary retention, jaundice, dysarthria, dystonia, changes in libido, irritability, and menstrual irregularities.

As with all benzodiazepines, paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, hallucinations, and other adverse behavioral effects may occur in rare instances and in a random fashion. Should these occur, use of the drug should be discontinued.

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** section).

DRUG ABUSE AND DEPENDENCE Withdrawal symptoms similar in character 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 which 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 upon 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. Evidence of physical dependency has been obtained in controlled studies that rely upon the finding that some patients exhibit withdrawal signs and symptoms upon drug discontinuation that cannot be attributed to the return of the psychopathology for which the benzodiazepine was initially prescribed. There is some evidence to suggest that gradual reduction of dosage will attenuate or eliminate these withdrawal phenomena. In most instances, the withdrawal phenomena have been 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 anticonvulsant 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 to such patients of habituation and dependence.

Controlled Substance Class DORMALIN is a controlled substance under the Controlled Substance Act and has been assigned by the Drug Enforcement Administration to Schedule IV.

OVERDOSAGE Overdosage of DORMALIN Tablets has not been reported. Manifestations of overdosage seen with other benzodiazepines include somnolence, confusion, and coma. In the event that an overdose occurs, the following is the recommended treatment. Respiration, pulse, and blood pressure should be monitored, as in all cases of drug overdosage. General supportive measures should be employed, along with immediate gastric lavage. Intravenous fluids should be administered and an adequate airway maintained. Hypotension may be treated with the use of Levophed® (levarterenol) or Aramine® (metaraminol). Dialysis is of limited value. Animal experiments suggest that forced diuresis or hemodialysis are probably of little value in treating overdosage. As with the management of intentional overdosing with any drug, it should be borne in mind that multiple agents may have been ingested.

The oral LD_{50} in mice was greater than 5,000 mg/kg.

DOSAGE AND ADMINISTRATION *Adults:* Initiate therapy at 15 mg until individual responses are determined. In some patients, the dose may then be reduced to 7.5 mg (half of a scored tablet).

Elderly and debilitated patients: Because the elderly and debilitated may be more sensitive to benzodiazepines, attempts to reduce the nightly dosage after the first one or two nights of therapy are suggested.

HOW SUPPLIED DORMALIN Tablets, 15 mg, capsule-shaped, light orange, slightly white speckled tablets, scored and impressed with the product identification number, 722 on each side of the score, on the scored side of the tablet, and the product name (DORMALIN), or "Schering" on the other; bottles of 100 (NDC 0085-0722-04) and 500 (NDC 0085-0722-07).

Store DORMALIN Tablets between 2° and 30°C (36° and 86°F).

Schering Corporation
Kenilworth, NJ 07033 USA

12 85

B-13758506

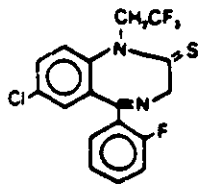
F-13758506

PRODUCT INFORMATION

DORMALIN®
brand of quazepam
Tablets

C-IV

DESCRIPTION DORMALIN (brand of quazepam) Tablets contain quazepam, a trifluoroethyl benzodiazepine hypnotic agent, having the chemical name 7-chloro-5-(*o*-fluorophenyl)-1,3-dihydro-1-(2,2,2-trifluoroethyl)-2*H*-1,4-benzodiazepine-2-thione and the following structural formula:



Quazepam has the empirical formula $C_{17}H_{11}ClF_6N_2S$, and a molecular weight of 386.8. It is a white crystalline compound, soluble in ethanol and insoluble in water.

Each DORMALIN Tablet contains 15 mg of quazepam.

The inactive ingredients for DORMALIN Tablets include cellulose, corn starch, FD&C Yellow No. 6 Al Lake, lactose, magnesium stearate, silicon dioxide, and sodium lauryl sulfate.

CLINICAL PHARMACOLOGY Central nervous system agents of the 1,4-benzodiazepine class presumably exert their effects by binding to stereo-specific receptors at several sites within the central nervous system (CNS). Their exact mechanism of action is unknown.

In a sleep laboratory study, DORMALIN Tablets significantly decreased sleep latency and total wake time, and significantly increased total sleep time and percent sleep time, for one or more nights. Quazepam 15 mg was effective on the first night of administration. Sleep latency, total wake time and wake time after sleep onset were still decreased and percent sleep time was still increased for several nights after the drug was discontinued. Percent slow wave sleep was decreased, and REM sleep was essentially unchanged. No transient sleep disturbance, such as "rebound insomnia", was observed after withdrawal of the drug in sleep laboratory studies in 12 patients using 15 mg doses.

In outpatient studies, DORMALIN Tablets improved all subjective measures of sleep including sleep induction time, duration of sleep, number of nocturnal awakenings, occurrence of early morning awakening, and sleep quality. Some effects were evident on the first night of administration of DORMALIN Tablets (sleep induction time, number of nocturnal awakenings, and duration of sleep). Residual medication effects ("hangover") were minimal.

Quazepam is rapidly absorbed (absorption half-life of about 30 minutes) and well absorbed from the gastrointestinal tract. The peak plasma concentration of quazepam is approximately 20 ng/ml after a 15 mg dose and is obtained at about 2 hours. Quazepam, the active parent compound, is extensively metabolized in the liver; two of the plasma metabolites are 2-oxoquazepam and N-desalkyl-2-oxoquazepam. All three compounds show pharmacological central nervous system activity in animals.

Following administration of ^{14}C-quazepam, approximately 31% of the dose appears in the urine and 23% in the feces over a five-day period; only trace amounts of unchanged drug are present in the urine.

The mean elimination half-life of quazepam and 2-oxoquazepam is 39 hours and that of N-desalkyl-2-oxoquazepam is 73 hours. Steady-state levels of quazepam and 2-oxoquazepam are attained by the seventh daily dose and that of N-desalkyl-2-oxoquazepam by the thirteenth daily dose.

The pharmacokinetics of quazepam and 2-oxoquazepam in geriatric subjects are comparable to those seen in young adults; as with desalkyl metabolites of other benzodiazepines, the elimination half-life of N-desalkyl-2-oxoquazepam in geriatric patients is about twice that of young adults.

The degree of plasma protein binding for quazepam and its two major metabolites is greater than 95%. The absorption, distribution, metabolism, and excretion of benzodiazepines may be altered in various disease states including alcoholism, impaired hepatic function, and impaired renal function.

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. When half-lives are long, drug or metabolites may accumulate during periods of nightly administration and 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 enhanced. 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 half-life of elimination, it is possible that a relative deficiency of the drug or its active metabolites (i.e., in relationship to the receptor site) may occur at some point in the interval between each night's use. This sequence of events may account for two clinical findings reported to occur after several weeks of nightly use of rapidly eliminated benzodiazepine hypnotics, namely, increased wakefulness during the last third of the night, and the appearance of increased signs of daytime anxiety in selected patients.

Quazepam crosses the placental barrier of mice. Quazepam, 2-oxoquazepam and N-desalkyl-2-oxoquazepam are present in breast milk of lactating women, but the total amount found in the milk represents only about 0.1% of the administered dose.

INDICATIONS AND USAGE DORMALIN Tablets are indicated for the treatment of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings. The effectiveness of DORMALIN has been established in placebo-controlled clinical studies of 5 nights duration in acute and chronic insomnia. The sustained effectiveness of DORMALIN has been established in chronic insomnia in a sleep lab (polysomnographic) study of 28 nights duration.

Because insomnia is often transient and intermittent, the prolonged administration of DORMALIN Tablets is generally not necessary or 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.

CONTRAINDICATIONS DORMALIN Tablets are contraindicated in patients with known hypersensitivity to this drug or other benzodiazepines, and in patients with established or suspected sleep apnea.

Usage in Pregnancy 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 following the ingestion of therapeutic doses of a benzodiazepine hypnotic during the last weeks of pregnancy.

DORMALIN Tablets are contraindicated in pregnancy because the potential risks outweigh the possible advantages of their use during this period. If there is a likelihood of the patient becoming pregnant while receiving DORMALIN she should be warned of the potential risk to the fetus. Patients should be instructed to discontinue the drug prior to becoming pregnant. The possibility that a woman of childbearing potential may be pregnant at the time of institution of therapy should be considered. (See Teratogenic Effects: Pregnancy Category X.)

WARNINGS Patients receiving benzodiazepines should be cautioned about possible combined effects with alcohol and other CNS depressants. Also, caution patients that an additive effect may occur if alcoholic beverages are consumed during the day following the use of benzodiazepines for nighttime sedation. The potential for this interaction continues for several days following their discontinuance until serum levels of psychoactive metabolites have declined.

Patients should also be cautioned about engaging in hazardous occupations requiring complete mental alertness such as operating machinery or driving a motor vehicle, after ingesting benzodiazepines, including potential impairment of the performance of such activities which may occur the day following ingestion.

Withdrawal symptoms of the type associated with sedatives/hypnotics (e.g., barbiturates, bromides, etc.) and alcohol have been reported after the discontinuation of benzodiazepines. While these symptoms have been more frequently reported after the discontinuation of excessive benzodiazepine doses, there have also been controlled studies demonstrating the occurrence of such symptoms after discontinuation of therapeutic doses of benzodiazepines, generally following prolonged use (but in some instances after periods as brief as six weeks). It is generally believed that the gradual reduction of dosage will diminish the occurrence of such symptoms (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). Consequently, elderly or debilitated patients and those with impaired renal or hepatic function should be cautioned about the risk and advised to monitor themselves for signs of excessive sedation or impaired coordination.

The possibility of respiratory depression in patients with chronic pulmonary insufficiency should be considered.

When benzodiazepines are administered to depressed patients, there is a risk that the signs and symptoms of depression may be intensified. Consequently, appropriate precautions (e.g., limiting the total prescription size and increased monitoring for suicidal ideation) should be considered.

Information for Patients It is suggested that physicians discuss the following information with patients. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

1. Inform your physician about any alcohol consumption and medicine you are taking now, including drugs you may buy without a prescription. Alcohol should generally 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. Inform your physician if you are nursing.
4. Until you experience how this medicine affects you, do not drive a car or operate potentially dangerous machinery, etc.
5. Benzodiazepines may cause daytime sedation, which may persist for several days following drug discontinuation.
6. Patients should be told not to increase the dose on their own and should inform their physician if they believe the drug "does not work anymore".
7. If benzodiazepines are taken on a prolonged and regular basis (even for periods as brief as six weeks), patients should be advised not to stop taking them abruptly or to decrease the dose without consulting their physician, because withdrawal symptoms may occur.

Laboratory Tests Laboratory tests are not ordinarily required in otherwise healthy patients when quazepam is used as recommended.

Drug Interactions The benzodiazepines, including DORMALIN Tablets, produce additive CNS depressant effects when co-administered with psychotropic medications, anticonvulsants, antihistamines, ethanol, and other drugs which produce CNS depression.

$$\sum_{i=1}^{n} x_i^4 - 4$$

NDA 18-708

AP/LTR

NDA 18-708

DEC 27 1985

Schering Corporation
Attention: Nelson H. Schimmel, M.D.
60 Orange Street
Bloomfield, New Jersey 07003

Dear Dr. Schimmel:

Please refer to your new drug application dated April 5, 1982, submitted pursuant to section 505(b) of the Federal Food, Drug and Cosmetic Act for Dormalin (quazepam) 15 mg tablets.

We also acknowledge receipt of your additional communications dated October 22, 1984, June 3 and September 5, 1985, and of your amendment dated November 25, 1985.

We have completed the review of this application, including the submitted draft labeling, and the application is approved, effective on the date of this letter. The changes agreed upon during a meeting on December 19, 1985, between representatives of Schering and this agency and listed in the addendum (q.v.), must be made in the labeling.

We also acknowledge your agreement to conduct the following studies in the postapproval period:

1. In your amendment dated November 25, 1985, you agreed to conduct an exploration of the applicability of aqueous buffers on solubilizing agents, and a study generating a pH-related dissolution profile. You agreed to use an ethanol media according to the parameters and specifications outlined in our letter dated August 30, 1985, until the revisions have been approved. We request that you submit the new information within 18 months.

2. In the meeting on December 19, 1985, you agreed to conduct a clinical study to evaluate the relationship between age and dose for quazepam. We request that you propose a design for an appropriate study for our review and comment within 12 months.

The labeling should be revised exactly as we have requested and twelve copies of the final printed version of the revised labeling (FPL) must be submitted to FDA prior to marketing. Marketing of the drug before the changes specified above are made and submitted to FDA, renders the product misbranded under 21 U.S.C. 352.

In addition, you may not legally market the drug until final rulemaking procedures for scheduling under the Controlled Substances Act are enacted by the Drug Enforcement Administration.

Should additional information relating to the safety and effectiveness of this drug product become available prior to our receipt of the final printed labeling, revision of that labeling may be required.

Please submit 12 copies of the revised final package insert and immediate container labels.

Also, please submit one market package of the drug which it is available.

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

Sincerely yours,

Robert Temple 12/20/85

Robert Temple, M.D.
Director
Office of Drug Research and Review
Center for Drugs and Biologics

Addendum: Final Labeling Draft

FINAL LABELING DRAFT

Addendum to approval letter for Dormalin (quazepam) Tablets, NDA 18-708:

Note: Any text noted as acceptable refers to wording for the draft package insert submitted with Schering's letter dated November 25, 1985. The page numbers listed below refer to the pages of that attachment unless noted otherwise.

DESCRIPTION: Acceptable.

CLINICAL PHARMACOLOGY:

Central nervous system agents of the 1,4-benzodiazepine class presumably exert their effects by binding to stereo-specific receptors at several sites within the central nervous system (CNS). Their exact mechanism of action is unknown.

In a sleep laboratory study, quazepam significantly decreased sleep latency, total wake time, and significantly increased total sleep time and percent sleep time for one or more nights. Quazepam 15 mg was effective on the first night of administration. Sleep latency, total wake time, and wake time after sleep onset were still decreased and percent sleep time was still increased for several nights after the drug was discontinued. Percent slow wave sleep was decreased, and REM sleep was essentially unchanged. No transient sleep disturbance, such as "rebound insomnia", was observed after withdrawal of the drug in sleep laboratory studies in 12 patients using 15 mg doses.

The paragraph beginning "In out-patient studies" on Page 2 and the next two paragraphs on Page 3 are acceptable. The last sentence of the third paragraph on Page 3 should be deleted. The last paragraph on page 3 is acceptable.

The first paragraph on page 4 should be revised as follows:

The degree of plasma protein binding for quazepam and its two major metabolites is greater than 95%. The absorption, distribution, metabolism, and excretion of benzodiazepines may be altered in various disease states including alcoholism, impaired hepatic function, and impaired renal function.

The last two paragraphs on page 4 should be deleted and replaced by the standard labeling proposed on page 3-FDA of the approvable letter dated August 30, 1985. These paragraphs begin with "The type and duration of hypnotic effects" and end with "anxiety in selected patients".

The last paragraph under Clinical Pharmacology appearing at the top of Page 5 is acceptable.

INDICATIONS AND USAGE:

Quazepam is indicated for the treatment of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings. The effectiveness of quazepam has been established in placebo controlled clinical studies of five nights duration in acute and chronic insomnia. The sustained effectiveness of Quazepam has been established in chronic insomnia in a sleep laboratory (polysomnograhic) study of 28 nights duration.

Because insomnia is often transient and intermittent, the prolonged administration of Dormalin (quazepam) is generally not necessary or 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 more specific treatment should be considered.

CONTRAINDICATIONS: Acceptable.

WARNINGS:

Patients receiving benzodiazepines should be cautioned about possible combined effects with alcohol and other CNS depressants. Also, caution patients that an additive effect may occur if alcoholic beverages are consumed during the day following the use of benzodiazepines for nighttime sedation. The potential for this interaction continues for several days following their discontinuance, until serum levels of psychoactive metabolites have declined.

Patients should be cautioned about engaging in hazardous occupations requiring complete mental alertness such as operating machinery or driving a motor vehicle after ingesting benzodiazepines, including potential impairment of the performance of such activities which may occur the day following ingestion.

The paragraph beginning "Withdrawal symptoms of the type" on page 4-FDA of the approvable letter dated August 30, 1985 should be incorporated as written.

PRECAUTIONS:

The three paragraphs in the General section listed on page 4-FDA and page 5-FDA of the approvable letter dated August 30, 1985 should be used with the following exceptions:

The first sentence of the first paragraph should state:

"Impaired motor and/or cognitive performance attributable to the accumulation of benzodiazepines and their active metabolites . . . ."

The first sentence of the first paragraph on page 5-FDA should state:

"When benzodiazepines are administered . . . ."

Information for Patients: It is suggested that physicians discuss the following information with patients. (This information to intended to aid in the safe and effective use of this drug. It is not a disclosure of all possible adverse or intended effects.)

Items 1 through 4 should be taken verbatim from those listed on page 5-FDA of the approvable letter dated August 30, 1985.

Item 5 should state:

"Benzodiazepines may cause daytime sedation, which may persist for several days following drug discontinuation."

Item 6 should state:

"Patients should be told not to increase the dose on their own and should inform their physician if they believe the drug does not work anymore."

Item 7 should state:

"If benzodiazepines are taken on a prolonged and regular basis (even for periods as brief as six weeks), patients should be advised not to stop taking them abruptly or to decrease the dose without consulting their physician, because withdrawal symptoms may occur".

Laboratory Tests: Acceptable.

Drug Interactions: Acceptable.

Carcinogenesis, Mutagenesis, etc.: Acceptable.

Teratogenic Effects: Acceptable.

Nonteratogenic Effects: Acceptable.

Labor and Delivery: Acceptable.

Nursing Mothers: Acceptable.

Pediatric Use: Acceptable.

ADVERSE REACTIONS:

Note: All of the text proposed in the Draft Labeling for the ADR section attached to the Schering letter dated November 25, 1985, up to the presentation of the table on Page 11, should be deleted and replaced by the following:

Adverse events most frequently encountered in patients treated with Dormalin are drowsiness and headache.

Accurate estimates of the incidence of adverse events associated with the use of any drug are difficult to obtain. Estimates are influenced by drug dose, detection technique, setting, physician judgments, etc. Consequently, the table below is presented solely to indicate the relative frequency of adverse events reported in representative controlled clinical studies conducted to evaluate the safety and efficacy of Dormalin. The figure cited cannot be used to predict precisely the incidence of such events during usual medical practice. These figures, also, cannot be compared with those obtained from other clinical studies involving related drug products and placebo.

The figures cited below are estimates of untoward clinical event incidences of 1% or greater among subjects who participated in the relatively short duration placebo-controlled clinical trials of Dormalin.

Insert the tables on Pages 11 and 12 with intervening text here.

Laboratory Tests: Acceptable.

Drug Interactions: Acceptable.

Carcinogenesis, Mutagenesis, etc.: Acceptable.

Teratogenic Effects: Acceptable.

Nonteratogenic Effects: Acceptable.

Labor and Delivery: Acceptable.

Nursing Mothers: Acceptable.

Pediatric Use: Acceptable.

ADVERSE REACTIONS:

Note: All of the text proposed in the Draft Labeling for the ADR section attached to the Schering letter dated November 25, 1985, up to the presentation of the table on Page 11, should be deleted and replaced by the following:

Adverse events most frequently encountered in patients treated with Dormalin are drowsiness and headache.

Accurate estimates of the incidence of adverse events associated with the use of any drug are difficult to obtain. Estimates are influenced by drug dose, detection technique, setting, physician judgments, etc. Consequently, the table below is presented solely to indicate the relative frequency of adverse events reported in representative controlled clinical studies conducted to evaluate the safety and efficacy of Dormalin. The figure cited cannot be used to predict precisely the incidence of such events during usual medical practice. These figures, also, cannot be compared with those obtained from other clinical studies involving related drug products and placebo.

The figures cited below are estimates of untoward clinical event incidences of 1% or greater among subjects who participated in the relatively short duration placebo-controlled clinical trials of Dormalin.

Insert the tables on Pages 11 and 12 with intervening text here.

The footnote at the bottom of Page 12 should be revised to include the following sentence:

"In addition, abnormalities in the following laboratory tests were observed in less than 1% of the patients evaluated: WBC count, platelet count, total protein, albumin, BUN, creatinine, total bilirubin, alkaline phosphatase, and SGPT."

After the footnote please follow with:

The following additional events occured among individuals receiving quazepam at doses equivalent to or greater than those recommended during its clinical testing and development. There is no way to establish whether or not the administration of Dormalin caused these events.

Hypokinesia, ataxia, confusion, incoordination, hyperkinesia, speech disorder, and tremor were reported.

Also, depression, nervousness, agitation, amnesia, anorexia, anxiety, apathy, euphoria, impotence, decreased libido, paranoid reaction, nightmares, abnormal thinking, abnormal taste perception, abnormal vision and cataract were reported.

Also reported were urinary incontinence, palpitations, nausea, constipation, diarrhea, abdominal pain, pruritus, rash, asthenia, and malaise.

Please delete the paragraph beginning "The following laboratory abnormalities".

The following list provides an overview of adverse experiences that have been reported and are considered to be reasonably related to the administration of benzodiazepines: incontinence, slurred speech, urinary retention, jaundice, dysarthria, dystonia, changes in libido, irritability, and menstrual irregularities.

As with all benzodiazepines, paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, hallucinations, and other adverse behavioral effects may occur in rare instances and in a random fashion. Should these occur, use of the drug should be discontinued.

There have been reports of withdrawal symptoms and signs 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 section).

DRUG ABUSE AND DEPENDENCE:

The text proposed in the approvable letter dated August 30, 1985, should be used except for the following modification in the first sentence:

"Withdrawal symptoms similar in character to those noted with sedative/hypnotics and alcohol have occurred following the abrupt discontinuation of drugs in the benzodiazepine class."

Controlled Substance Class: Acceptable.

OVERDOSAGE: Acceptable.

DOSAGE AND ADMINISTRATION:

Adults - Initiate therapy at 15 mg until individual responses are determined. In some patients, the dose may then be reduced to 7.5 mg (half of a scored tablet).

Elderly and debilitated patients - Because the elderly and debilitated may be more sensitive to benzodiazepines, attempts to reduce the nightly dosage after the first one or two nights of therapy are suggested.

HOW SUPPLIED: Acceptable.

Addendum (DOC#3741p)

PI

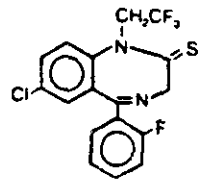
F-13758506

PRODUCT INFORMATION

DORMALIN®
brand of quazepam
Tablets

C IV

DESCRIPTION DORMALIN (brand of quazepam) Tablets contain quazepam, a trifluoroethyl benzodiazepine hypnotic agent, having the chemical name 7-chloro-5-(*o*-fluorophenyl)-1,3-dihydro-1-(2,2,2-*trifluoroethyl*)-2*H*-1,4-*benzodiazepine*-2-thione and the following structural formula:



[illegible] the empirical formula $C_{17}H_{11}ClF_4N_2S$, and a molecular weight of 386.8. It is a white crystalline compound, soluble in ethanol and insoluble in water.

Each DORMALIN tablet contains 15 mg of quazepam.

The inactive ingredients for DORMALIN Tablets include cellulose, corn starch, FD&C Yellow No. 6 Al Lake, lactose, magnesium stearate, silicon dioxide, and sodium lauryl sulfate.

CLINICAL PHARMACOLOGY Central nervous system agents of the 1,4-benzodiazepine class presumably exert their effects by binding to stereo-specific receptors at several sites within the *central nervous system (CNS). Their exact mechanism of action* is unknown.

In a sleep laboratory study, DORMALIN Tablets significantly decreased sleep latency and total wake time, and significantly increased total sleep time and percent sleep time, *for one or more* nights. Quazepam 15 mg was effective on the first night of administration. Sleep latency, total wake time and wake time after sleep onset were still decreased and percent sleep time was still increased for several nights after the drug was discontinued. Percent slow wave sleep was decreased, and REM sleep was essentially unchanged. No transient sleep disturbance, such as "rebound insomnia", was observed after withdrawal of the drug in sleep laboratory studies in 12 patients using 15 mg doses.

In outpatient studies, DORMALIN Tablets improved all subjective measures of sleep including sleep induction time, duration of sleep, number of nocturnal awakenings, occurrence of early [illegible] the effectiveness of DORMALIN Tablets (sleep induction time, number of nocturnal awakenings, and duration of sleep). Residual medication effects ("hangover") were minimal.

Quazepam is rapidly (*absorption half-life of about 30 minutes*) and well absorbed from the gastrointestinal tract. The peak plasma concentration of quazepam is approximately 20 ng/ml after a 15 mg dose and is obtained at about 2 hours. Quazepam, the active parent compound, is extensively metabolized in the liver; two of the plasma metabolites are 2-oxoquazepam and N-desalkyl-2-oxoquazepam. All three compounds show pharmacological central nervous system activity in animals.

Following administration of ^{14}C-quazepam, approximately 31% of the dose appears in the urine and 23% in the feces over a five-day period; only trace amounts of unchanged drug are present in the urine.

The mean elimination half-life of quazepam and 2-oxoquazepam *is 39 hours and that of N-desalkyl-2-oxoquazepam* is 73 hours. Steady-state levels of quazepam and 2-oxoquazepam are attained by the seventh daily dose and that of N-desalkyl-2-oxoquazepam by the thirteenth daily dose.

The pharmacokinetics of quazepam and 2-oxoquazepam in geriatric subjects are comparable to those seen in young adults; as with desalkyl metabolites of other benzodiazepines, the elimination half-life of N-desalkyl-2-oxoquazepam in geriatric patients is about twice that of young adults.

The degree of plasma protein binding for quazepam and its two major metabolites *is greater than 95%. The absorption,* distribution, metabolism, and excretion of benzodiazepines may be altered in various disease states including alcoholism, impaired hepatic function, and impaired renal function.

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. When half-lives are long, drug or metabolites may accumulate during periods of nightly administration and 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 enhanced. In contrast, if half-lives are short, drug and metabolites will be cleared before the next dose is ingested, and carryover 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 half-life of elimination, it is possible that a relative deficiency of the drug or its active metabolites (i.e., in relationship to the receptor site) may occur at some point in the interval between each night's use. This sequence of events may account for two clinical findings reported to occur after several weeks of nightly use of rapidly eliminated benzodiazepine hypnotics, namely, increased wakefulness during the last third of the night, and the appearance of increased signs of daytime anxiety in selected patients.

Quazepam crosses the placental barrier of mice. Quazepam, 2-oxoquazepam and N-desalkyl-2-oxoquazepam are present in breast milk of lactating women, but the total amount found in the milk represents only about 0.1% of the administered dose.

INDICATIONS AND USAGE DORMALIN Tablets are indicated for the treatment of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings. The effectiveness of DORMALIN has been established in placebo-controlled clinical studies of 5 nights duration in acute and chronic insomnia. The sustained effectiveness of DORMALIN has been established in chronic insomnia in a sleep lab (polysomnographic) study of 28 nights duration.

Because insomnia is often transient and intermittent, the prolonged administration of DORMALIN Tablets is generally not necessary or 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.

CONTRAINDICATIONS DORMALIN Tablets are contraindicated in patients with known hypersensitivity to this drug or other benzodiazepines, and in patients with established or suspected sleep apnea.

Usage in Pregnancy 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 following the ingestion of therapeutic doses of a benzodiazepine hypnotic during the last weeks of pregnancy.

DORMALIN Tablets are contraindicated in pregnancy because *the potential risks outweigh the possible advantages of their use* during this period. If there is a likelihood of the patient becoming pregnant while receiving DORMALIN she should be warned of the potential risk to the fetus. Patients should be instructed to discontinue the drug prior to *becoming pregnant. The possibility* that a woman of childbearing potential may be pregnant at the time of institution of therapy should be considered. (See **Teratogenic Effects: Pregnancy Category X.**)

WARNINGS *Patients receiving benzodiazepines should be* cautioned about possible combined effects with alcohol and other CNS depressants. Also, caution patients that an additive effect may occur if alcoholic beverages are consumed during the day following the use of benzodiazepines for nighttime sedation. The potential for this interaction continues for several days following their discontinuance until serum levels of psychoactive metabolites have declined.

Patients should also be cautioned about engaging in hazardous occupations requiring complete mental alertness such as operating machinery or driving a motor vehicle, after ingesting benzodiazepines, including potential impairment of the performance of such activities which may occur the day following ingestion.

Withdrawal symptoms of the type associated with sedatives/hypnotics (e.g., barbiturates, bromides, etc.) and alcohol have been reported after the discontinuation of benzodiazepines. While these symptoms have been more frequently reported after the discontinuation of excessive benzodiazepine doses, there have also been controlled studies demonstrating the occurrence of such symptoms after discontinuation of therapeutic doses of benzodiazepines, generally following prolonged use (but in some instances after periods as brief as six weeks). It is generally *believed* that the gradual reduction of dosage will diminish the occurrence of such symptoms (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). Consequently, elderly or debilitated patients and those with impaired renal or hepatic function should be cautioned about the risk and advised to monitor themselves for signs of excessive sedation or impaired coordination.

The possibility of respiratory depression in patients with chronic pulmonary insufficiency should be considered.

When benzodiazepines are administered to depressed patients, there is a risk that the signs and symptoms of depression may be intensified. Consequently, appropriate precautions (e.g., limiting the total prescription size and increased monitoring for suicidal ideation) should be considered.

Information for Patients It is suggested that physicians discuss the following information with patients. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

1. Inform your physician about any alcohol consumption and medicine you are taking now, including drugs you may buy without a prescription. Alcohol should generally not be used during treatment with hypnotics.
2. Consult 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. Inform your physician if you are nursing.
4. Until you experience how this medicine affects you, do not drive a car or operate potentially *dangerous machinery, etc.*
5. Benzodiazepines may cause daytime sedation, which may persist for several days following drug discontinuation.
6. Patients should be told not to increase the dose on their own and should inform their physician if they believe the drug "does not work anymore".
7. If benzodiazepines are taken on a prolonged and regular basis (even for periods as brief as six weeks), patients should be advised not to stop taking them abruptly or to decrease the dose without consulting their physician, because withdrawal symptoms may occur.

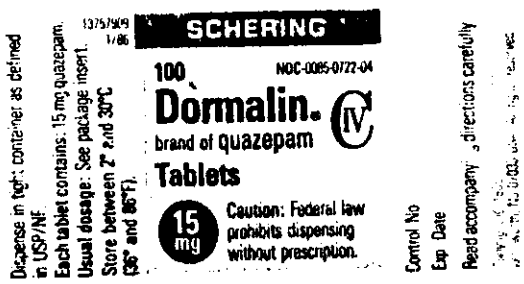
Laboratory Tests Laboratory tests are not ordinarily required in otherwise healthy patients when quazepam is used as recommended.

Drug Interactions The benzodiazepines, including DORMALIN Tablets, produce additive CNS depressant effects when coadministered with psychotropic medications, anticonvulsants, antihistaminics, ethanol, and other drugs which produce CNS depression.

DORMALIN Tablets, 15 mg
Label for 14, professional sample

LBL

DORMALIN Tablets, 15 mg
Label for 100



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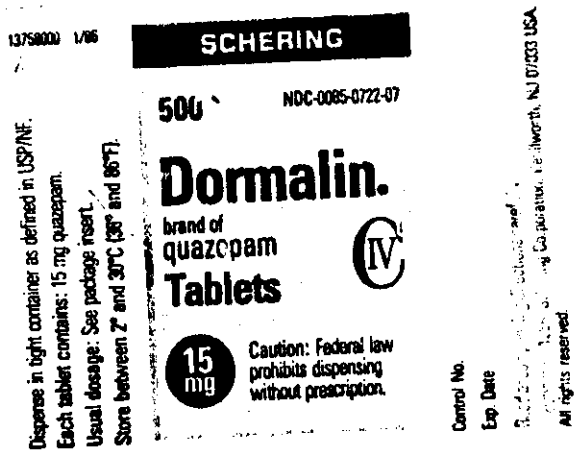
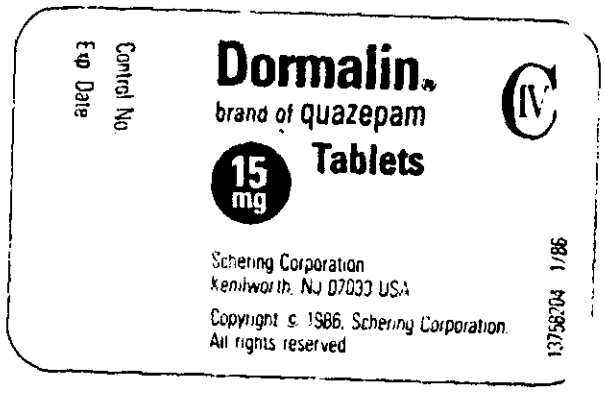
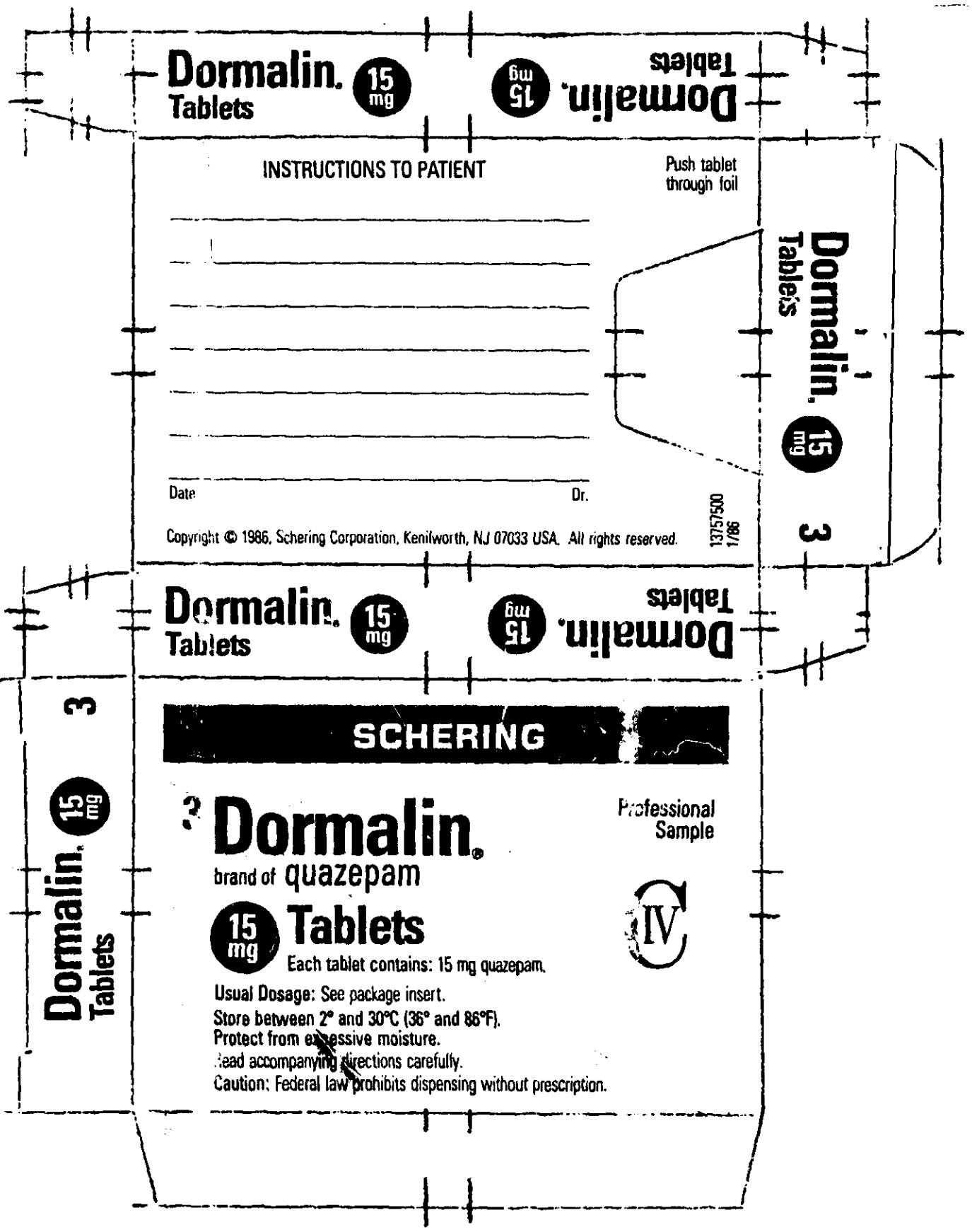
Label for 500



DORMALIN Tablets
Backing



DORMALIN Tablets
Carton for 3, professional sample



5

MED. REVIEW

Medical Officer's Review of NDA 16-705
(Original Submission: April 5, 1982)

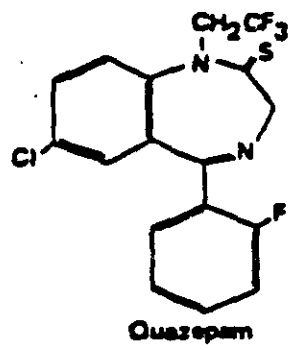
Sponsor: Schering Corporation
Bloomfield, NJ

8 1982

Name of Drug:

Code designation: SCH 16134
USAN: quazepam (Q)
Trade name: not yet available
Chemical: 7-chloro-5 (o-fluorophenyl)-1,3-dihydro-1-(2,2,2-trifluoroethyl-2H-1,4-benzodiazepin-2-thione)

Structural Formula:



Quazepam

Pharmacologic Category: benzodiazepine hypnotic

Dosage Forms: quazepam 15 mg tablets

Route of Administration: oral

Related IND: ———

Chemist's Review (V. Iliev, Ph.D., 6/6/82): Approval recommended from standpoint of manufacturing controls.

Pharmacology (Refer to review by R. Hollenbeck, Ph.D., of 10/14/82):

The main behavioral effect of quazepam in animals is drowsiness and sedation. The reviewing pharmacologist recommends that the application for quazepam be approved.

Review of Bioavailability Studies [refer to review of 4/26/83 by N.E. Useeney, Ph.D. (HFN-525)]:

The application is acceptable to the Division of Biopharmaceutics, if the firm agrees to further dissolution testing as outlined in the final section of recommendations.

Pharmacokinetic profile:

Quazepam is rapidly absorbed from the G.I. tract. The plasma concentrations of quazepam are proportional to the administered dose; peak levels of approximately 20 ng/ml after a 15 mg dose and 40 ng/ml after a 30 mg dose are obtained at about 2 hrs.

Quazepam is extensively metabolized; two major plasma metabolites, 2-oxoquazepam (formed by the substitution of oxygen for sulfur) and N-desalkylflurazepam (formed by the N-dealkylation of 2-oxoquazepam) are pharmacologically active.

The elimination half-life of quazepam or 2-oxoquazepam is about 40 hours and that of N-desalkylflurazepam is about 70 hours. After multiple-dosing, the observed steady-state levels of quazepam and 2-oxoquazepam are attained by the seventh daily dose and that of N-desalkylflurazepam by the thirteenth daily dose.

The elimination half-life of N-desalkylflurazepam in geriatric patients is about twice that of young adults.

Quazepam, 2-oxoquazepam and N-desalkylflurazepam are present in breast milk of lactating women.

Drug Abuse Consulting Review [refer to review of 5/3/83 by F.J. Vocci, Jr., Ph.D. (HFN-123)]:

The sponsor has not demonstrated that quazepam is significantly different from other benzodiazepines with respect to abuse potential.

Clinical doses, up to 30 mg a night for 4 weeks, do not procuce a significant withdrawal syndrome.

On April 26, 1983, the Drug Abuse Advisory Committee agreed that quazepam be placed in Schedule IV of the Controlled Substances Act.

I. Controlled Clinical Studies

A. Sleep Lab Studies:

C&C-077-01 (in volume 1.36): by Gerald W. Vogel, Director, Sleep Lab, GAMHI, Atlanta.

Objective: to evaluate the short-term (5 nights) safety and [illegible] efficacy of quazepam (Q) 15 mg and 30 mg and flurazepam (F) 15 mg and 30 mg in volunteers with chronic insomnia.

Experimental Design:

The study involved a parallel group design in which treatment was administered in a double-blind fashion to 24 healthy subjects (8 men and 16 women), ages 24 to 60 yrs, with both subjective and objective insomnia. Subjects complained of taking 45 minutes or more to fall asleep and sleeping for fewer than 6.5 hours at least 4 nights/week for 3 months or more prior to the pre-treatment interview. Objective insomnia was measured during nights 2-4 in a four consecutive night placebo baseline; TST of less than 400 minutes in 450 minutes of total bedtime on any two of baseline nights 2-4.

Schedule was as follows:

Night 1: placebo (adaptation to sleep lab)
Night 2-4: placebo (baseline)
Night 5-9: drug (either Q15, Q30, F15 or F30 mg)
Night 10-11: placebo (drug withdrawal)

24 subjects were randomly assigned to 4 treatment groups (6/group).

Measurements:

The following polygraphic efficacy variables were scored:

1. TST (total sleep time)
2. % sleep (% of total bedtime occupied by sleep)
3. TWT (total wake time)
4. Wake time in each third of the night
5. Persistent sleep latency (time from "lights out" to the onset of the first sleep that persisted for at least 10 consecutive minutes)
6. Wake time after persistent sleep onset
7. Number of awakenings $\geq$ 30 seconds duration

Efficacy and safety were assessed both within and between treatment groups.

Results: (refer to following tables in Volume 1.36)

#2 (p.104)
" (p.105)
" (p.106)
" (p.107)
" (p.108)
" (p.109)
" (p.110)
" (p.113)
" (p.114)

TABLE # 2
PAGE 1

QUAZEPAM STUDY 3

POLYGRAPHIC EFFICACY VARIABLE - ACROSS ALL SUBJECTS

TOTAL SLEEP TIME (MINUTES)

S#	BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN
QUAZEPAM 15mg.					
1	344.2	423.5	427.7	425.5	427.0
2	377.7	432.5	437.1	437.0	430.8
3	365.2	371.5	322.2	397.5	407.0
4	397.0	413.0	403.9	385.0	401.0
5	401.0	390.5	386.4	428.0	421.2
6	380.0	399.5	400.4	405.5	383.5
MN	377.5	405.1	396.3	413.1	411.8
P(diff. from BSL)		**	NS	**	**
QUAZEPAM 30mg.					
7	321.2	405.0	426.9	420.0	416.2
8	389.5	429.5	428.2	429.0	429.0
9	362.7	404.0	385.8	396.5	391.2
10	365.8	427.0	435.8	442.0	433.8
11	330.8	372.5	380.1	394.0	404.0
12	385.0	434.0	413.1	423.5	424.0
	359.2	412.0	411.6	417.5	416.4
		***	***	***	***

S#	BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN
FLURAZEPAM 15mg.					
13	380.3	397.5	399.6	405.0	386.0
14	361.5	403.0	402.0	387.5	373.0
15	399.7	412.5	417.6	417.0	417.5
16	374.3	399.5	391.6	410.0	412.2
17	402.0	437.0	427.8	422.5	425.2
18	375.7	393.0	413.0	367.0	380.8
MN	382.2	407.1	408.6	401.5	399.1
P(diff. from BSL)		***	***	**	**
FLURAZEPAM 30mg.					
19	335.3	283.0	398.6	420.0	423.5
20	327.2	429.5	420.5	289.5	339.5
21	327.0	352.0	365.1	357.5	364.0
22	359.2	358.0	356.5	391.5	376.5
23	357.8	373.0	370.9	412.0	409.2
24	370.8	404.5	407.5	383.5	361.5
	346.2	366.7	386.5	375.7	379.0
		NS	**	NS	*

P(difference between QUAZEPAM change from BSL. and FLURAZEPAM change from BSL.)
(The BSL MEAN entries represent P(diff. between Q BSL and F BSL))

	BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN
15mg	NS	NS	NS	NS	NS
30mg	NS	NS	NS	NS	NS

Within treatment differences assessed by matched pair t-test, one tailed for baseline vs drug, two tailed for baseline vs post drug. Across treatment difference assessed by two tailed, non-paired t-test.

KEY:

NS	Not Significant at 0.10 level
*	Probability < 0.10
**	Probability < 0.05
***	Probability < 0.01

TABLE # 2
PAGE 2

QUAZEPAM STUDY 3

POLYGRAPHIC EFFICACY VARIABLE - ACROSS ALL SUBJECTS

PERCENT SLEEP

S#	BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN	S#	BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN
	QUAZEPAM 15mg.						QUAZEPAM 30mg.				
1	76.5	94.1	95.0	94.6	94.9	7	71.4	89.9	94.8	93.3	93.5
2	84.2	96.1	97.1	97.1	95.7	8	86.5	95.1	95.1	95.3	95.3
3	81.1	82.6	71.6	88.3	90.4	9	80.6	89.8	85.7	88.0	86.9
4	88.2	91.8	89.7	85.6	89.1	10	81.1	94.9	96.8	98.2	96.4
5	89.1	86.8	85.9	95.1	93.6	11	73.6	82.8	84.5	87.6	89.8
6	84.4	88.8	89.0	90.1	85.2	12	85.6	96.4	91.8	94.0	94.2
MN	83.9	90.0	88.1	91.8	91.5		79.8	91.5	91.5	92.7	92.5
P(diff. from BSL)		**	NS	**	**			***	***	***	***
	FLURAZEPAM 15mg.						FLURAZEPAM 30mg.				
13	84.5	88.4	88.8	90.0	85.8	19	74.5	62.9	88.6	93.3	94.1
14	80.3	89.4	89.3	86.1	82.9	20	72.7	95.4	93.4	64.3	75.4
15	88.8	91.7	92.8	92.7	92.8	21	72.7	78.2	81.2	79.4	80.9
16	83.1	88.5	87.0	91.1	91.6	22	79.8	79.6	79.2	87.0	83.7
17	89.3	97.1	95.1	93.9	94.5	23	79.5	82.9	82.4	91.6	90.9
18	83.5	87.3	91.8	81.6	84.6	24	82.4	89.9	90.6	85.2	80.3
MN	84.9	90.4	90.8	89.2	88.7		76.9	81.5	85.9	83.5	84.2
P(diff. from BSL)		***	***	**	**			NS	**	NS	*

P(difference between QUAZEPAM change from BSL. and FLURAZEPAM change from BSL.)
(The BSL MEAN entries represent P(diff. between Q BSL and F BSL))

	BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN		BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN
15mg	NS	NS	NS	NS	NS	30mg	NS	NS	NS	NS	NS

Within treatment differences assessed by matched pair t-test, one tailed for baseline vs drug, two tailed for baseline vs post drug. Across treatment difference assessed by two tailed, non-paired t-test.

KEY:

NS	Not Significant at 0.10 level
*	Probability < 0.10
**	Probability < 0.05
***	Probability < 0.01

TABLE # 2
PAGE 3

QUAZEPAM STUDY 1

POLYGRAPHIC EFFICACY VARIABLE - ACROSS ALL SUBJECTS

TOTAL WAKE TIME (MINUTES)

S#	BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN
	QUAZEPAM 15mg.				
1	102.3	22.0	17.0	22.0	20.5
2	66.0	13.5	10.7	11.0	16.5
3	80.0	72.5	122.6	45.0	32.8
4	49.7	30.0	40.1	61.0	43.8
5	47.5	58.0	60.5	13.0	22.8
6	66.0	44.0	42.5	37.0	60.2
MN	68.6	40.0	48.9	31.5	32.8
P(diff. from BSL)		**	NS	**	**
	FLURAZEPAM 15mg.				
13	68.3	50.5	49.2	42.5	62.2
14	88.3	46.5	47.6	62.5	76.2
15	43.5	31.0	25.2	26.5	21.5
16	72.0	50.0	54.6	37.0	32.0
17	44.7	10.5	19.7	21.5	20.5
18	73.0	57.0	35.3	77.5	65.0
MN	65.0	40.9	38.6	44.6	46.2
P(diff. from BSL)		***	***	**	**

S#	BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN
	QUAZEPAM 30mg.				
7	127.7	45.0	21.4	24.5	30.0
8	52.8	12.0	15.5	14.5	15.0
9	81.0	33.5	56.9	49.5	53.0
10	81.8	17.0	10.4	7.0	14.5
11	114.2	72.5	66.2	53.5	43.5
12	59.7	10.5	33.5	24.5	23.2
	86.2	31.8	34.0	28.9	29.9
		***	***	***	***
	FLURAZEPAM 30mg.				
19	113.5	166.0	49.5	26.0	23.8
20	116.7	16.5	27.1	155.0	104.5
21	122.5	94.0	82.7	90.5	85.0
22	88.8	91.0	91.0	56.5	71.0
23	90.2	71.0	75.5	36.5	58.5
24	75.8	42.0	39.0	63.0	85.8
	101.2	80.1	60.8	71.2	68.1
		NS	**	NS	*

P(difference between QUAZEPAM change from BSL. and FLURAZEPAM change from BSL.)
(The BSL MEAN entries represent P(diff. between Q BSL and F BSL))

	BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN		BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN
15mg	NS	NS	NS	NS	NS	30mg	NS	NS	NS	NS	NS

Within treatment differences assessed by matched pair t-test, one tailed for baseline vs drug, two tailed for baseline vs post drug. Across treatment difference assessed by two tailed, non-paired t-test.

KEY:

NS	Not Significant at 0.10 level
*	Probability < 0.10
**	Probability < 0.05
***	Probability < 0.01

TABLE # 2
PAGE 4

QUAZEPAM STUDY 3

POLYGRAPHIC EFFICACY VARIABLE - ACROSS ALL SUBJECTS

WAKE TIME (MINUTES) DURING FIRST THIRD OF NIGHT

S#	BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN	S#	BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN
	QUAZEPAM 15mg.						QUAZEPAM 30mg.				
1	68.2	8.5	6.2	4.5	5.5	7	96.0	29.0	10.8	8.0	9.5
2	20.0	11.5	6.3	3.5	4.8	8	25.5	6.0	8.7	5.0	6.8
3	67.3	69.0	102.3	41.5	29.2	9	68.2	30.0	43.1	30.5	15.8
4	21.2	26.0	32.0	37.0	29.5	10	47.5	17.0	8.8	4.0	9.8
5	20.3	37.5	20.3	4.5	6.8	11	91.3	65.0	63.1	48.0	35.0
6	19.8	9.5	7.8	8.0	11.8	12	24.5	10.5	8.1	10.5	9.0
MN	36.1	27.0	29.2	16.5	14.6		58.8	26.2	23.8	17.7	17.6
P(diff. from BSL)		NS	NS	NS	*			***	**	**	**
	FLURAZEPAM 15mg.						FLURAZEPAM 30mg.				
13	19.8	25.0	23.7	22.0	18.2	19	53.8	43.0	14.3	8.5	5.2
14	60.5	26.0	25.4	25.5	43.8	20	37.5	5.0	9.1	36.5	23.5
15	24.0	24.5	20.1	13.0	12.2	21	83.0	76.0	64.0	74.5	60.0
16	52.0	15.0	19.4	10.5	9.8	22	29.7	29.5	30.7	22.0	34.8
17	44.5	10.5	18.6	20.5	19.2	23	46.2	59.5	66.9	15.0	16.2
18	36.2	20.5	18.6	50.5	47.0	24	55.2	33.5	27.9	28.5	50.8
MN	39.5	20.2	21.0	23.7	25.0		50.9	41.1	35.5	30.8	31.8
P(diff. from BSL)		**	**	NS	NS			*	*	**	*

P(difference between QUAZEPAM change from BSL. and FLURAZEPAM change from BSL.)
(The BSL MEAN entries represent P(diff. between Q BSL and F BSL))

	BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN		BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN
15mg	NS	NS	NS	NS	NS	30mg	NS	**	NS	NS	

Within treatment differences assessed by matched pair t-test, one tailed for baseline vs drug, two tailed for baseline vs post drug. Across treatment difference assessed by two tailed, non-paired t-test.

KEY:

NS	Not Significant at 0.10 level
*	Probability < 0.10
**	Probability < 0.05
***	Probability < 0.01

TABLE # 2
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QUAZEPAM STUDY 3

POLYGRAPHIC EFFICACY VARIABLE - ACROSS ALL SUBJECTS

WAKE TIME (MINUTES) DURING MIDDLE THIRD OF NIGHT

S#	BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN	S#	BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN
	QUAZEPAM 15mg.						QUAZEPAM 30mg.				
1	10.2	2.5	2.2	8.0	6.5	7	6.7	9.5	4.5	8.5	5.0
2	.5	1.0	.4	.0	.0	8	18.5	6.0	4.0	4.5	3.3
3	7.5	1.0	17.8	2.5	3.0	9	7.5	2.5	5.9	16.0	14.2
4	3.3	2.5	3.5	16.0	9.2	10	6.3	.0	.6	.0	2.2
5	10.8	7.5	24.8	.0	3.5	11	7.2	5.0	1.9	2.0	3.8
6	11.2	12.0	6.1	16.5	3.2	12	9.7	.0	14.6	.0	6.0
MN	7.2	4.4	9.1	7.2	5.1		9.3	3.8	5.2	5.2	5.8
P(diff. from BSL)		*	NS	NS	NS			**	*	NS	NS
	FLURAZEPAM 15mg.						FLURAZEPAM 30mg.				
13	26.0	6.5	6.5	14.0	37.8	19	18.3	61.0	15.1	8.0	11.0
14	8.2	15.5	13.1	5.5	4.8	20	68.7	.0	2.3	1.5	4.8
15	4.5	3.5	3.2	6.0	3.5	21	27.3	8.5	8.3	5.5	9.2
16	8.5	22.5	18.0	21.5	18.0	22	7.0	42.5	24.9	23.5	14.8
17	.2	.0	.0	1.0	.5	23	25.2	2.0	3.6	1.0	6.8
18	17.8	10.5	5.8	6.5	4.0	24	10.3	6.0	7.3	34.0	20.2
MN	10.9	9.8	7.8	9.1	11.4		26.1	20.0	10.2	12.2	11.1
P(diff. from BSL)		NS	NS	NS	NS			NS	NS	NS	NS

P(difference between QUAZEPAM change from BSL. and FLURAZEPAM change from BSL.)
(The BSL MEAN entries represent P(diff. between Q BSL and F BSL))

	BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN		BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN
15mg	NS	NS	NS	NS	NS	30mg	NS	NS	NS	NS	NS

Within treatment differences assessed by matched pair t-test, one tailed for baseline vs drug, two tailed for baseline vs post drug. Across treatment difference assessed by two tailed, non-paired t-test.

KEY:

NS Not Significant at 0.10 level
* Probability < 0.10
** Probability < 0.05
*** Probability < 0.01

TABLE # 2
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QUAZEPAM STUDY 3

POLYGRAPHIC EFFICACY VARIABLE - ACROSS ALL SUBJECTS

WAKE TIME (MINUTES) DURING LAST THIRD OF NIGHT

S#	BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN	S#	BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN
	QUAZEPAM 15mg.						QUAZEPAM 30mg.				
1	24.0	11.0	8.6	9.5	8.5	7	25.0	6.5	6.1	8.0	15.5
2	45.5	1.0	4.0	7.5	11.8	8	8.8	.0	2.8	5.0	5.0
3	5.2	2.5	2.5	1.0	.5	9	5.3	1.0	7.9	3.0	3.0
4	25.2	1.5	4.6	8.0	5.0	10	8.0	.0	1.0	3.0	7.5
5	16.3	13.0	15.4	8.5	12.5	11	15.7	2.5	1.2	3.5	4.8
6	35.0	22.5	28.6	12.5	40.2	12	25.5	.0	10.8	14.0	8.2
MN	25.2	8.6	10.6	7.8	13.1		18.1	1.7	5.0	6.1	6.5
P(diff. from BSL)		**	**	**	*			***	**	**	**
	FLURAZEPAM 15mg.						FLURAZEPAM 30mg.				
13	22.5	19.0	19.0	6.5	6.2	19	41.3	62.0	20.1	9.5	7.5
14	19.7	5.0	9.1	31.5	27.8	20	10.5	11.5	15.7	117.0	76.2
15	15.0	3.0	1.9	7.5	5.8	21	12.2	9.5	10.4	10.5	15.8
16	11.5	12.5	17.2	5.0	4.2	22	52.2	19.0	35.4	11.0	21.5
17	.0	.0	1.1	.0	.8	23	18.8	9.5	5.0	20.5	15.5
18	19.0	26.0	10.9	20.5	14.0	24	10.3	2.5	3.8	.5	14.9
MN	14.6	10.9	9.9	11.8	9.8		24.2	19.0	15.1	28.2	25.2
P(diff. from BSL)		NS	*	NS	NS			NS	**	NS	NS

P(difference between QUAZEPAM change from BSL. and FLURAZEPAM change from BSL.)
(The BSL MEAN entries represent P(diff. between Q BSL and F BSL))

	BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN		BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN
15mg	NS	NS	NS	**	NS	30mg	NS	NS	NS	NS	NS

Within treatment differences assessed by matched pair t-test, one tailed for baseline vs drug, two tailed for baseline vs post drug. Across treatment difference assessed by two tailed, non-paired t-test.

KEY:

NS	Not Significant at 0.10 level
*	Probability < 0.10
**	Probability < 0.05
***	Probability < 0.01

TABLE # 2
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QUAZEPAM STUDY 3

POLYGRAPHIC EFFICACY VARIABLE - ACROSS ALL SUBJECTS

WAKE TIME (MINUTES) AFTER PERSISTENT SLEEP ONSET

S#	BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN	S#	BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN
	QUAZEPAM 15mg.						QUAZEPAM 30mg.				
1	88.8	19.0	14.2	18.0	16.0	7	32.0	16.0	11.0	18.5	22.3
2	48.3	2.0	4.4	7.5	11.8	8	36.0	6.5	9.7	12.0	13.2
3	13.8	3.5	4.3	3.5	3.8	9	13.5	4.0	20.0	29.5	20.3
4	30.0	4.0	9.7	27.0	16.5	10	42.0	10.5	5.2	3.5	5.2
5	29.0	20.5	44.5	10.0	18.0	11	28.7	8.0	5.2	9.0	10.2
6	54.3	35.5	36.8	30.5	54.0	12	48.5	3.5	28.8	20.0	12.2
MN	44.4	14.1	19.0	16.1	20.0		33.4	8.1	13.3	15.4	15.5
P(diff. from BSL)		**	**	**	*			***	***	*	**
S#	FLURAZEPAM 15mg.					S#	FLURAZEPAM 30mg.				
13	55.3	36.0	36.5	29.0	48.2	19	73.3	158.5	44.2	17.5	18.5
14	30.5	21.0	25.2	39.5	35.8	20	93.7	11.5	19.8	118.5	81.3
15	23.7	6.5	5.1	13.5	10.8	21	48.8	21.0	21.6	22.0	31.2
16	37.8	38.0	44.1	29.0	24.5	22	70.2	62.0	70.2	39.5	56.2
17	.3	.0	1.1	2.0	1.8	23	44.3	11.5	11.8	23.5	28.2
18	44.5	41.5	21.8	27.0	18.0	24	22.3	8.5	11.3	35.5	38.3
MN	31.9	23.8	22.3	23.3	23.2		58.8	45.5	29.8	42.8	41.7
P(diff. from BSL)		**	*	NS	NS			NS	**	NS	NS

P(difference between QUAZEPAM change from BSL. and FLURAZEPAM change from BSL.)
(The BSL MEAN entries represent P(diff. between Q BSL and F BSL))

	BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN		BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN
15mg	NS	*	NS	NS	NS	30mg	*	NS	NS	NS	NS

Within treatment differences assessed by matched pair t-test, one tailed for baseline vs drug, two tailed for baseline vs post drug. Across treatment difference assessed by two tailed, non-paired t-test.

KEY:

NS Not Significant at 0.10 level
* Probability < 0.10
** Probability < 0.05
*** Probability < 0.01

TABLE # 2
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QUAZEPAM STUDY 3

POLYGRAPHIC EFFICACY VARIABLE - ACROSS ALL SUBJECTS

LATENCY (MINUTES) TO PERSISTENT SLEEP ONSET

S#	BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN	S#	BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN
	QUAZEPAM 15mg.						QUAZEPAM 30mg.				
1	21.8	3.0	2.8	5.0	5.0	7	96.2	29.0	10.4	6.0	8.0
2	17.8	12.5	7.0	3.5	4.8	8	20.7	5.5	7.0	2.5	1.8
3	67.0	69.0	121.4	41.5	29.0	9	67.5	30.0	38.8	20.5	32.2
4	30.3	26.5	33.7	47.5	35.5	10	43.8	6.5	6.8	3.5	9.8
5	18.8	56.5	19.8	3.0	5.0	11	88.0	65.5	61.4	49.5	35.3
6	12.8	11.5	6.7	9.5	7.8	12	12.2	7.5	4.9	4.5	5.0
MN	28.1	29.8	31.9	18.3	14.5		54.7	24.0	21.6	14.4	15.4
P(diff. from BSL)		NS	NS	NS	*			***	**	**	**
	FLURAZEPAM 15mg.						FLURAZEPAM 30mg.				
13	13.7	18.0	14.6	13.5	15.0	19	41.2	15.0	7.8	12.5	7.2
14	59.8	25.5	24.9	25.0	42.0	20	26.8	10.5	9.0	39.0	26.8
15	23.8	33.5	25.3	13.0	11.0	21	77.8	73.0	62.5	70.5	55.0
16	38.0	12.0	12.6	12.5	10.2	22	18.8	29.0	24.4	25.5	23.2
17	46.3	11.0	21.3	19.5	21.0	23	47.5	59.5	64.7	13.0	17.2
18	29.8	19.5	14.3	57.0	51.2	24	59.5	38.5	32.8	37.5	52.8
MN	35.2	19.9	18.8	23.4	25.1		45.3	37.6	33.5	33.0	30.4
P(diff. from BSL)		*	**	NS	NS			NS	*	NS	*

P(difference between QUAZEPAM change from BSL. and FLURAZEPAM change from BSL.)
(The BSL MEAN entries represent P(diff. between Q BSL and F BSL))

	BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN		BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN
15mg	NS	NS	NS	NS	NS	30mg	NS	*	NS	*	*

Within treatment differences assessed by matched pair t-test, one tailed for baseline vs drug, two tailed for baseline vs post drug. Across treatment difference assessed by two tailed, non-paired t-test.

KEY:

NS	Not Significant at 0.10 level
*	Probability < 0.10
**	Probability < 0.05
***	Probability < 0.01

TABLE # 2
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QUAZEPAM STUDY 3

POLYGRAPHIC EFFICACY VARIABLE - ACROSS ALL SUBJECTS

NUMBER OF AWAKENINGS

S#	BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN
	QUAZEPAM 15mg.				
1	26.7	22.0	14.8	10.0	10.5
2	7.7	5.0	5.0	5.0	6.0
3	9.0	4.0	5.0	5.0	4.5
4	16.0	6.0	7.2	17.0	13.5
5	10.3	17.0	11.0	2.0	8.0
6	9.0	9.0	9.8	18.0	11.0
MN	13.1	10.5	8.8	9.5	8.9
P(diff. from BSL)		NS	**	NS	NS
	FLURAZEPAM 15mg.				
13	11.0	10.0	10.0	8.0	7.5
14	18.3	14.0	16.4	24.0	23.5
15	15.7	9.0	4.0	16.0	11.0
16	11.7	12.0	16.6	12.0	11.0
17	2.0	1.0	1.4	3.0	5.0
18	17.3	20.0	14.6	12.0	12.0
MN	12.7	11.0	10.5	12.5	11.7
P(diff. from BSL)		NS	NS	NS	NS

S#	BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN
	QUAZEPAM 30mg.				
7	5.3	7.0	3.8	5.0	5.0
8	15.0	2.0	5.8	6.0	7.0
9	7.3	4.0	7.4	10.0	10.0
10	19.3	3.0	3.4	6.0	8.5
11	8.7	6.0	2.8	6.0	6.5
12	30.7	3.0	8.0	2.0	5.5
	14.4	4.2	5.2	5.8	7.1
		**	**	NS	NS
	FLURAZEPAM 30mg.				
19	12.3	35.0	16.2	15.0	12.5
20	17.0	1.0	3.4	9.0	10.5
21	23.3	18.0	17.6	16.0	16.5
22	14.3	8.0	9.2	11.0	9.0
23	10.0	4.0	5.8	6.0	9.0
24	14.0	9.0	9.2	9.0	17.5
	15.2	12.5	10.2	11.0	12.5
		NS	**	**	NS

P(difference between QUAZEPAM change from BSL. and FLURAZEPAM change from BSL.)
(The BSL MEAN entries represent P(diff. between Q BSL and F BSL))

	BSL MEAN	DRUG NT 1	DRUG MEAN	P-DRUG NT 1	P-DRUG MEAN
15mg	NS	NS	NS	NS	NS
30mg	NS	NS	NS	NS	NS

Within treatment differences assessed by matched pair t-test, one tailed for baseline vs drug, two tailed for baseline vs post drug. Across treatment difference assessed by two tailed, non-paired t-test.

KEY:

NS Not Significant at 0.10 level
* Probability < 0.10
** Probability < 0.05
*** Probability < 0.01

Efficacy:

Q15: On the first drug night, Q15 did not shorten sleep latency, but it did increase TST. On the mean drug night, Q15 did not shorten sleep latency or increase TST, but did decrease the number of awakenings, decreased wake time after sleep onset, and decreased wake time in last third of night.

Compared with baseline values, on the first post-drug night and on the mean post-drug night, TST increased, TWT decreased, wake time in the last third of the night decreased, and wake time after persistent sleep onset decreased. Thus, there was no evidence of a rebound insomnia but positive evidence for a hypnotic carryover effect.

Q30: On the first drug night as well as on the mean drug night, Q30 significantly improved all efficacy variables; sleep latency was shortened and TST increased. All indicators of sleep maintenance were improved; TWT and wake time in each third of the night were decreased, as well as the number of awakenings.

During the post-drug period, Q30 did not produce rebound insomnia but a hypnotic carryover effect was evident.

Safety:

Other than the possibility of some daytime drowsiness during withdrawal, no adverse effects were observed. Clinical lab tests included CBC, urinalysis, SMA-12 and EKG.

Comments:

Within treatment, analysis indicated that Q30 decreased sleep latency, increased sleep time, and improved sleep maintenance. After 5 nights of continuous administration, Q15 and Q30 produced a post-drug hypnotic carryover effect, and no rebound insomnia.

Some paradoxical results noted between quazepam and flurazepam at the 15mg and 30mg doses may be due to the small sample in each treatment group (n=6/group).

Objective: To assess and compare hypnotic effects of 30 mg quazepam and 0.5 mg triazolam on the sleep of chronic insomniacs who were otherwise free of medical or major psychological problems.

Experimental Design:

Parallel group design in which treatment was administered for 14 nights to 12 subjects (8 men and 4 women), who ranged in age from 3[illegible] to 55 yrs, with chronic insomnia. Subjectively, each subject took at least 45 minutes to fall asleep and slept less than 6 hours. On EEG-sleep recordings, on any two consecutive nights during nights 2-4, each subject had to sleep no more than 390 minutes during the 450 min recording period.

Schedule as follows:

Night 1: placebo (adaptation)
Night 2-4: placebo (baseline)
Night 5-18: drug (either quazepam 30 mg or triazolam 0.5 mg)
(Nights 5-7, in sleep lab; 8-14, at home; 15, reception;
16-18, intermediate effects)
Night 19-25: placebo (withdrawal)

Measurements:

1. TST (minutes)
2. Sleep efficiency (%): ratio of TST to total time in bed
3. Sleep latency (minutes): sleep induction time measured from "lights out" to first minute or more of stage 2 sleep
4. Total nocturnal wake time (minutes)
5. Duration of wakefulness and number of awakenings of 5 min or more in each third of night

Results: (refer to following tables in Volume 1.40)

I (p.18)
II (p.19)
III (p.20)
VI (p.23)

Average TST for Q30 baseline period was 347.59 minutes. During the first three nights (short term), Q30 increased it to 363.09 min and to 392.51 minutes during nights 16-18 (intermediate term). After 14 nights on Q30 and upon abrupt withdrawal, TST declined to 383.83 min on night 19 (Table VI) and to 361.22 min on night 20. On night 25, TST was 341.94 min, near baseline average.

Triazolam 0.5 mg increased TST from a baseline average of 363.33 min to 415.55 min on night 5. The average for nights 5-7 (short term) was 406.16 min, but decreased to 399.35 min for nights 16-18 (intermediate term). On the first withdrawal night 19, TST rapidly decreased to 213.39 min, and gradually reached baseline average of 368.89 min on night 25 (Table VI).

Upon comparing efficacy of Q30 and T 0.5mg, increase in TST from baseline for quazepam was 12.92% vs 9.61% for triazolam. On the first withdrawal night 19, increase in TST for quazepam was 10.42%; it decreased by 41.26% for triazolam (Table III).

At baseline, sleep latency for quazepam was 41.37 minutes and decreased to 31.77 minutes on the first night of administration and decreased further to 28.7 minutes (nights 5-7) and 25.16 minutes (nights 16-18). Thus, hypnotic efficacy increased progressively. In contrast, triazolam decreased sleep latency from baseline 32.58 min to 22.27 min, maintained it at 24.4 min, and slightly increased it to 27.18 minutes; and, on the first withdrawal night (night 19) it increased to 85.06 minutes demonstrating rebound insomnia (Table III).

When comparing efficacy of the two drugs tested, Q decreased nocturnal wakefulness from baseline by 44.75% after 2 weeks administration and by 35.89% on the first withdrawal night. Triazolam decreased it by 45.01% after 2 weeks and increased nocturnal wakefulness by 190.67% on the first withdrawal night (night 19 - Table III).

The short and intermediate-term (2 weeks) effects of 15 mg quazepam were examined on the sleep of 6 chronic insomniacs. Each subject was studied for 22 consecutive nights (4 baseline; 14 drug; 4 placebo withdrawal). The following data were obtained:

1. Sleep induction time (sleep latency): time from "lights out" until stage 2 sleep
2. TST
3. Sleep efficiency: ratio of TST to total time in bed
4. No of awakenings of 10 sec or more
5. Duration of wakefulness and number of awakenings of 10 sec or more in each third of the night

Results:

TST increased progressively on the first 3 nights of quazepam administration from 416.8 min to 429.2 to 432.7 minutes (Table III). Following drug withdrawal, TST returned to baseline values without any evidence for rebound insomnia.

In this study, 15 mg quazepam did not decrease sleep latency; however, the pre-treatment average sleep latency was only 27.4 minutes. Nevertheless, there was a significant decrease in wakefulness during the first third of the night.

There was poor correlation between the subjective and objective data.

three nights of its administration, this decrease did not reach statistical significance. After 2 weeks on quazepam the sleep latency was 28.8 minutes and on withdrawal it remained at about this level, 25.1 minutes. Quazepam, however, was active in the first third of the night. It significantly decreased the total period of wakefulness during the first third of the night immediately after it was started, from an average of 30.4 minutes during the baseline period to 17.8 minutes on nights 5, 6, and 7. Again, tolerance developed to this effect so that at the end of the two weeks of drug administration, the total period of wakefulness during the first third of the night on nights 15, 16 and 17 was 26.1

Table III — *Total sleep time on individual study nights*

Night	Total Sleep Time (min)	
	Mean	S.D.
1	385.6	45.4
2	413.7	26.9
3	385.0	44.9
4	372.0	34.9
5	418.8	26.9
6	429.2	12.1
7	432.7	19.3
Home Nights 8-14		
15	409.2	46.4
16	420.3	34.1
17	400.8	37.1
18	422.3	18.7
19	398.2	39.1
20	390.2	42.3
21	417.2	30.0
22	383.7	41.4

minutes — a value not significantly different from baseline. During the second third of the night, quazepam significantly decreased the duration of wakefulness throughout the period of its administration, and an even greater decrease in the duration of wakefulness was observed in the third third of the night, but here, because of the great variability of the data, the decrease did not reach statistical significance. During the withdrawal period, the duration of wakefulness returned to baseline values in all three thirds of the night. In spite of the decrease in the total duration of wakefulness during the night, the number of awakenings of 10 seconds or more in duration each night was not significantly changed by 15 mg. of quazepam.

Quazepam produced significant differences in the duration and percentages of the different stages of NREM sleep (Table II). There was a progressive decrease in the duration and percentage of stage 1 sleep during the two-week drug administration period which persisted throughout the drug-withdrawal period. The duration and percentage of stage 2 sleep in contrast, rose progressively during the 2-week drug administra-

Objective: to evaluate effects of 15 mg and 30 mg quazepam (Q) and 30 mg flurazepam (F) on 17 insomniacs (22-60 yrs), administered drug for 28 consecutive nights, followed by a 15-night withdrawal period.

Study Design: 17 subjects were assigned to one of 3 drug groups in a double-blind manner:

Q 15 mg -- 5 subjects
Q 30 mg -- 6 subjects
F 30 mg -- 6 subjects

Schedule was as follows:

Nights 1-4:	on placebo (in sleep lab)
Nights 5-7:	active drug (in sleep lab)
Nights 8-14:	active drug (at home)
Night 15:	active drug (readaptation lab)
Nights 16-18:	active drug (in sleep lab)
Nights 19-28:	active drug (at home)
Night 29:	active drug (readaptation lab)
Nights 30-32:	active drug (in sleep lab)
Nights 33-47:	on placebo (withdrawal effects in lab)

Results:

Q 30 mg (Table 3): TWT decreased by 57.4% from 70.7 minutes (baseline) to 30.1 minutes (nights 5-7). On nights 16-18, TWT decreased from baseline by 30.3% to 49.3 minutes. On nights 30-32, TWT decreased from baseline by 22.6% to 54.7 minutes. Following drug withdrawal (nights 33-35), TWT remained below baseline, 49.3 minutes vs. 70.7 minutes.

F 30 mg (Table 4): TWT decreased by 51.1% from 100.6 minutes (baseline) to 49.2 min (nights 5-7). On nights 16-18, TWT decreased from baseline by 42.7% to 57.6 min. On nights 30-32, TWT decreased from baseline by 35.1% to 65.3 min. Following withdrawal (nights 45-47), TWT approximated baseline values, 103.3 min vs. 100.6 min.

Quazepam 15 mg (Table 5): TWT decreased by 37.5% from 95.2 min (baseline) to 59.5 min (nights 5-7). On nights 16-18, TWT decreased from baseline by 41.8% to 55.4 min. On nights 30-32, TWT decreased from baseline by 29.6% to 67.0 min. Following withdrawal (nights 33-35), TWT remained below baseline, 71.9 min vs. 95.2 min.

TABLE 3

Effectiveness of Quazepam 30 mg for Sleep Induction and Maintenance: Short-, Intermediate- and Long-term Drug Administration

	BSLN 2-4	DRUG 5-7	DRUG 16-18	DRUG 30-32	WD/L 33-35	WD/L 45-47
Sleep latency (min)	35.9	18.7	29.5	34.9	27.3	37.2
Wake time after sleep onset (min)	34.8	11.4†	19.8	19.9	22.0	21.9
Total wake time (min)	70.7	30.1†	49.3	54.7	49.3	59.1
Total no. of wakes	13.4	8.5†	11.4	11.6	11.5	10.2*
Per cent sleep time	85.3	93.7†	89.7	88.6	89.7	87.7
Per cent wake time by thirds of night						
1st	8.9	4.4†	3.0*	3.2†	3.5†	1.9†
2nd	4.4	2.3	4.8	3.9	7.6	6.0
3rd	10.5	3.7	5.1	7.9	5.3	6.7

All numbers represent mean values for the 6 subjects.

† $p<0.01$
* $p<0.05$

TABLE 3

Effectiveness of Quazepam 30 mg for Sleep Induction and Maintenance: Short-, Intermediate- and Long-term Drug Administration

	BSLN 2-4	DRUG 5-7	DRUG 16-18	DRUG 30-32	WDWL. 33-35	WDWL. 45-47
Sleep latency (min)	35.9	18.7	29.5	34.9	27.3	37.2
Wake time after sleep onset (min)	34.8	11.4†	19.8	19.8	22.0	21.9
Total wake time (min)	70.7	30.1†	49.3	54.7	49.3	59.1
Total no. of wakes	13.4	8.5†	11.4	11.6	11.5	10.2*
Per cent sleep time	85.3	93.7†	89.7	88.6	89.7	87.7
Per cent wake time by thirds of night						
1st	8.9	1.4†	3.0*	1.2†	1.5†	1.9†
2nd	4.4	2.3	4.8	3.9	7.6	6.0
3rd	10.5	3.7	5.1	7.9	5.3	6.7

All numbers represent mean values for the 6 subjects.

† $p<0.01$
* $p<0.05$

TABLE 4

Effectiveness of Flurazepam 30 mg for Sleep Induction and Maintenance: Short-, Intermediate- and Long-term Drug Administration

	BSLN 2-4	DRUG 5-7	DRUG 16-18	DRUG 30-32	WDWL 33-35	WDWL 45-47
Sleep latency (min)	55.7	31.1†	28.8†	40.9	42.7	63.6
Wake time after sleep onset (min)	44.9	18.1†	28.8	24.4*	44.7	39.7
Total wake time (min)	100.6	49.2†	57.6†	65.3*	87.4	103.3
Total no. of wakes	15.4	12.7	16.2	16.2	17.1	15.4
Per cent sleep time	79.0	89.7†	88.0†	86.4*	81.8	78.5
Per cent wake time by thirds of night						
1st	8.3	1.9	4.7	3.3	8.9	8.4
2nd	9.4	5.1	4.7	4.3	10.6	5.9
3rd	14.7	5.2	9.8	8.8	11.7	14.6

All numbers represent mean values for the 6 subjects.

† $p<0.01$
* $p<0.05$

TABLE 5

Effectiveness of Quazepam 15 mg for Sleep Induction and Maintenance: Short-, Intermediate- and Long-term Drug Administration

	BSLN 2-4	DRUG 5-7	DRUG 16-18	DRUG 30-32	WDWL 33-35	WDWL 45-47
Sleep latency (min)	57.3	37.3	27.0†	39.1	44.5	53.7
Wake time after sleep onset (min)	37.9	22.2	28.6	27.9	27.4	23.6
Total wake time (min)	95.2	59.5†	55.4†	67.0*	71.9	77.3
Total no. of wakes	14.7	11.5	12.9	13.1	13.8	12.5
Per cent sleep time	80.2	87.6†	88.5†	86.0*	85.0	83.9
Per cent wake time by *thirds of night*						
1st	4.9	2.9	2.4	1.5*	1.5*	1.7*
2nd	11.3	3.?	4.0	8.0	5.6	4.5
3rd	10.2	8.6	11.9	8.8	11.1	9.6

All numbers represent mean values for the 5 subjects.

† $p<0.01$
* $p<0.05$

These studies
may be regarded as pivotal to establishing that quazepam 30 mg significantly improved all efficacy variables: sleep latency was shortened and TST increased; TWT and wake time in each third of the night were decreased, as well as the number of awakenings. However, in both and studies, quazepam 15 mg did not shorten sleep latency, but did increase TST. In Kales' study, on baseline nights (2-4), sleep latency was 57.3 minutes. It decreased to 37.3 minutes after quazepam 15 mg (nights 5-7); with intermediate-term administration of Q 15 mg (nights 16-18), sleep latency was 27.6 minutes ($p < 0.01$). On nights 30-32 (long-term administration), sleep latency was 39.9 minutes.

There was no indication of rebound insomnia during the 15-day withdrawal period.

B. <u>Short-term (5 night) Clinical Efficacy Studies of Quazepam (Q) 30 mg</u>

<u>Objective</u>: to assess the safety and efficacy of 30 mg quazepam vs. placebo in out-patient insomniacs, as determined by daily, subjective self-evaluations by the patients and overall evaluations by patients and by investigators.

<u>Design</u>: balanced-parallel-groups; double-blind, placebo-controlled, randomized. For the first 3 nights, patients took placebo under single-blind conditions; for the last 5 nights, patients took either Q 30 mg or placebo.

<u>Measurement</u>: Efficacy was evaluated using responses on post-sleep questionnaires, and the physicians' and patients' global evaluations at the end of the study. Safety was evaluated using items 6, 7, and 8 on the daily post-sleep questionnaire and ADR, ECG and lab tests pre- and post-treatment.

<u>Results</u>:

Four U.S. investigators used a common protocol
) involving 178 outpatients.
was <u>terminated</u> after 6 months "because the investigator had only 14 valid cases (5 on Q30 and 9 on placebo)" and was unable to fulfill the protocol requirement of 60 cases.

These studies
may be regarded as pivotal to establishing that quazepam 30 mg significantly improved all efficacy variables: sleep latency was shortened and TST increased; TWT and wake time in each third of the night were decreased, as well as the number of awakenings. However, in both and studies, quazepam 15 mg did not shorten sleep latency, but did increase TST. In Kales' study, on baseline nights (2-4), sleep latency was 57.3 minutes. It decreased to 37.3 minutes after quazepam 15 mg (nights 5-7); with intermediate-term administration of Q 15 mg (nights 16-18), sleep latency was 27.0 minutes ($p < 0.01$). On nights 30-32 (long-term administration), sleep latency was 39.9 minutes.

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B. <u>Short-term (5 night) Clinical Efficacy Studies of Quazepam (Q) 30 mg</u>

<u>Objective</u>: to assess the safety and efficacy of 30 mg quazepam vs. placebo in out-patient insomniacs, as determined by daily, subjective self-evaluations by the patients and overall evaluations by patients and by investigators.

<u>Design</u>: balanced-parallel-groups; double-blind, placebo-controlled, randomized. For the first 3 nights, patients took placebo under single-blind conditions; for the last 5 nights, patients took either Q 30 mg or placebo.

<u>Measurements</u>: Efficacy was evaluated using responses on post-sleep questionnaires, and the physicians' and patients' global evaluations at the end of the study. Safety was evaluated using items 6, 7, and 8 on the daily post-sleep questionnaire and ADR, ECG and lab tests pre- and post-treatment.

<u>Results</u>:

Four U.S. investigators used a common protocol
) involving 176 outpatients.
was <u>terminated</u> after 6 months "because the investigator had only 14 valid cases (5 on Q30 and 9 on placebo)" and was unable to fulfill the protocol requirement of 60 cases.

In) involving 58 outpatients (29 on Q30 and 29 on placebo), no significant treatment differences in favor of Q30 were observed.

a total of 50 outpatients (24 on Q30 and 26 on placebo) were evaluated for efficacy and 57 patients (28 on Q and 29 on P) were evaluated for safety. Responses for the 6 efficacy items from the daily sleep questionnaire are summarized in Table 3. The results during the treatment period were significant on 3 or 4 nights, and consistently favored Q over placebo.

There was less morning alertness in the Q group (Table 4).

The most frequently reported ADR was daytime somnolence (16/28 on Q30 vs. 4/29 on placebo). Two patients (#44, #54) discontinued Quazepam on the last study night due to ADR (somnolence) and one patient (#12) took only 15 mg Q on the last study night due to drowsiness the previous night.

, a total of 56 patients were evaluated (28 on Q and 28 on placebo). Four patients dropped out after the second night of treatment: two were Q-treated patients (#27, #56). Adverse reactions reported by #27 (daytime somnolence) and by #56 (daytime somnolence, hypokinesia and difficulty concentrating).

In the placebo group, patient #7 dropped out because of "treatment failure" and #31 reported daytime somnolence and nausea.

Responses for items 1 to 5 and item 9 on the post-sleep questionnaire, are tabulated on Table 4. Q30 induced sleep more quickly than placebo, and maintained sleep longer with fewer awakenings.

22 patients reported AR: 13 in the Q group and 9 in the placebo group. AR attributed to treatment are shown in Table 6. Daytime somnolence was reported most frequently: 12/26 in the Q-treated group and 5/28 in the placebo group.

Using the same protocol,
at the . 47 patients were evaluated for efficacy (24 on Q30 and 23 on placebo). One Q-treated patient (#25) dropped out because of severe daytime somnolence. Two placebo-treated patients dropped out: #3 because of a death in the family and #9 because of treatment failure. 15 patients reported AR (13 in Q group and 2 in placebo group). 10/24 on Q30 reported daytime somnolence and only 1/23 on placebo (See Table 6).

The responses for the 6 efficacy items from the daily sleep questionnaire are summarized in Table 4. Q30 was shown to be superior to placebo with respect to nocturnal awakenings, but not as regards to sleep latency or TST.

TABLE 3

SHORT TERM CLINICAL STUDY OF SCH 14134 IN OUTPATIENTS WITH INSOMNIA
STUDY NUMBER
SUMMARY OF RESULTS FOR THE PATIENT'S SLEEP QUESTIONNIRE
EFFICACY EVALUATIONS

		STUDY NIGHTS								
		BASELINE			DOUBLE-BLIND TREATMENT					OVERALL TREATMENT
QUESTION(NO.)	N*	1	2	3	4	5	6	7	8	4-8
SLEEP INDUCTION TIME(1)										
QUAZEPAM	24	2.9	3.3	3.1	4.0	4.2	3.8	4.1	3.9	4.0
PLACEBO	26	3.0	2.4	3.1	2.8	3.2	2.9	2.8	3.0	3.0
P-VALUE		NS	<.05	NS	.01	<.05	<.10	.01	.05	<.01
TOTAL SLEEP TIME(2)										
QUAZEPAM	24	2.0	2.5	2.2	1.3	3.5	3.4	3.6	3.4	3.4
PLACEBO	26	2.4	1.8	2.2	2.3	2.8	2.3	2.6	2.8	2.6
P-VALUE		NS	<.05	NS	<.05	NS	<.05	<.05	NS	<.01
NOCTURNAL AWAKENINGS(3)										
QUAZEPAM	24	3.0	3.2	3.2	3.0	3.7	3.6	4.0	3.5	3.7
PLACEBO	26	2.0	2.7	2.0	3.0	3.1	2.7	3.2	3.2	3.0
P-VALUE		NS	<.10	NS	<.05	.05	<.01	<.05	NS	<.01
EARLY MORNING AWAKEN.(4)										
QUAZEPAM	24	0.4	0.3	0.4	0.0	0.0	0.7	0.9	0.0	0.0
PLACEBO	26	0.6	0.2	0.1	0.4	0.7	0.6	0.5	0.5	0.5
P-VALUE		<.10	NS	NS	<.01	NS	NS	<.01	<.05	<.01
SLEEP QUALITY(5)										
QUAZEPAM	24	2.6	2.0	2.0	3.7	3.0	3.7	4.1	3.5	3.8
PLACEBO	26	3.0	2.4	2.0	3.0	3.3	2.9	3.2	3.2	3.1
P-VALUE		NS	<.10	NS	<.05	<.10	<.05	<.05	NS	.01
PATIENT RATING(9)										
QUAZEPAM	24	1.4	1.0	1.5	2.5	2.6	2.7	2.7	2.3	2.6
PLACEBO	26	2.0	1.4	1.0	1.0	2.2	2.0	2.1	2.1	2.0
P-VALUE		<.05	NS	NS	<.05	NS	<.05	<.05	NS	<.05

NS = NOT SIGNIFICANT (P>.10).
HIGHER SCORE INDICATES BETTER RESPONSE.

TABLE 4

SHORT TERM CLINICAL STUDY OF SCH 16134 IN OUTPATIENTS WITH INSOMNIA
STUDY NUMBER
SUMMARY OF RESULTS FOR THE PATIENT'S SLEEP QUESTIONNAIRE
SAFETY EVALUATIONS

		STUDY NIGHTS								
		BASELINE			DOUBLE-BLIND TREATMENT					OVERALL TREATMENT
QUESTION(NO.)	N*	1	2	3	4	5	6	7	8	4-8
EASE OF AWAKENING(6)										
QUAZEPAM	24	3.1	3.3	3.0	3.1	2.8	2.7	2.3	2.7	2.7
PLACEBO	26	3.1	3.1	3.0	3.0	3.2	3.0	2.8	2.8	3.0
P-VALUE		NS	NS	NS	NS	NS	NS	<.10	NS	NS
MORNING ALERTNESS(7)										
QUAZEPAM	24	2.6	2.8	2.6	2.9	2.5	2.4	2.2	2.4	2.5
PLACEBO	26	3.0	2.9	2.9	3.0	3.2	3.0	3.1	3.0	3.1
P-VALUE		<.10	NS	NS	NS	.01	<.05	<.01	<.05	<.01
NIGHTMARES(8)										
QUAZEPAM	24	0.7	0.9	1.0	0.9	0.9	1.0	1.0	0.9	0.9
PLACEBO	26	0.9	0.7	0.9	0.8	0.9	0.9	0.9	0.9	0.9
P-VALUE		NS	NS	NS	NS	NS	NS	NS	NS	NS

NS = NOT SIGNIFICANT(P>.10).
HIGHER SCORE INDICATES BETTER RESPONSE.

TABLE 4

SHORT TERM CLINICAL STUDY OF SCH 16134 IN OUTPATIENTS WITH INSOMNIA
STUDY NO.

Summary of Results for the Patient's Sleep Questionnaire

Safety Evaluations

Question (No.)	N*	Study Nights: Baseline 1	2	3	Double-Blind Treatment 4	5	6	7	8	Overall Treatment 4-8
Ease of Awakening (6)										
Quazepam	38	3.1	3.8	3.1	2.6	3.8	2.9	2.9	2.9	2.8
Placebo	38	3.1	3.8	2.9	3.8	2.8	3.1	3.1	2.9	2.9
P-Value		NS	NS	NS	<.10	NS	NS	NS	NS	NS
Morning Alertness (7)										
Quazepam	38	2.8	2.8	2.8	2.8	2.9	2.9	2.8	2.9	2.8
Placebo	38	2.7	2.8	3.0	2.8	2.7	3.8	3.1	2.9	2.9
P-Value		NS	NS	NS	NS	NS	NS	NS	NS	NS
Nightmares (8)										
Quazepam	38	0.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8
Placebo	38	1.8	1.8	1.8	0.9	0.9	0.9	0.9	0.9	0.9
P-Value		NS	NS	NS	NS	NS	NS	NS	NS	NS

* Refer to Table A2 (Appendix) for patients who missed answering one or more questions on any of the nights in the study.
NS = Not Significant (p>.10).
Higher score indicates better response.

Table 8. Number of Patients in Each Treatment Group Reporting Those Adverse Experiences Attributed to Treatment by the Project Physician

Adverse Experience	Number of Patients*	
	Quazepam	Placebo
Daytime somnolence†	10	1
Coordination abnormal	3	0
Dizziness	2	0
Headache	1	0
Mouth dry	0	1
Nausea	2	0
Tremor	1	0
Blurred vision	1	0

* Some patients reported more than one adverse experience.
† Probability of no difference between the groups: P<.01.

Table 4. Mean Values for Items 1 to 5 and Item 9 on the Patients' Postsleep Questionnaires for All Eight Study Nights and for the Overall Treatment Period.*

	Baseline Nights			Treatment Nights					
	1	2	3	4	5	6	7	8	Overall
Sleep Induction Time†									
Quazepam	3.2	3.0	3.0	3.4	3.8	4.0	3.7	3.9	3.7
Placebo	2.7	3.1	3.0	3.1	3.2	3.4	3.5	3.3	3.3
"p"	NSD	NSD	NSD	NSD	<.10	<.10	NSD	NSD	NSD
Total Sleep Time§									
Quazepam	2.0	2.6	2.8	3.2	3.5	3.5	3.8	3.2	3.4
Placebo	2.3	2.5	2.7	2.7	2.8	3.1	2.5	2.7	2.8
"p"	NSD	NSD	NSD	NSD	NSD	NSD	<.01	NSD	<.05
Nocturnal Awakenings¶									
Quazepam	2.9	3.2	3.4	4.3	4.4	4.4	4.3	4.3	4.3
Placebo	2.6	2.9	3.2	2.0	3.2	3.4	3.0	3.1	3.2
"p"	NSD	NSD	NSD	<.01	<.01	<.01	<.01	<.01	<.01
Early Morning Awakening#									
Quazepam	0.3	0.5	0.7	0.8	0.8	0.9	1.0	0.8	0.8
Placebo	0.5	0.5	0.7	0.7	0.8	0.6	0.6	0.6	0.7
"p"	<.10	NSD	NSD	NSD	NSD	<.10	<.01	<.10	<.05
Sleep Quality††									
Quazepam	2.8	2.9	3.3	3.9	4.0	4.0	4.1	3.9	4.0
Placebo	2.5	3.0	3.4	3.3	3.5	3.3	3.3	3.2	3.4
"p"	NSD	NSD	NSD	<.10	<.10	<.05	<.05	.05	<.01
Rating of Medication‡‡									
Quazepam	1.7	1.7	1.9	2.7	2.9	2.8	2.9	3.0	2.9
Placebo	1.6	1.7	2.1	2.0	2.3	2.2	2.2	2.3	2.2
"p"	NSD	NSD	NSD	<.05	<.05	.05	<.05	<.05	<.01

* "p" is the probability of no difference between the groups. NSD = no significant difference.

† Rated on a scale of 1 to 5: 5 = 0 to 15 min, 4 = 16 to 30 min, 3 = 31 to 45 min, 2 = 46 to 60 min, 1 = >60 min.

§ Rated on a scale of 1 to 5: 5 = >8 hr, 4 = 7.1 to 8 hr, 3 = 6.1 to 7 hr, 2 = 5.1 to 6 hr, 1 = 5 hr or less.

¶ Rated on a scale of 1 to 5: 5 = no awakenings, 4 = 1, 3 = 2 or 3, 2 = 4 or 5, 1 = 6 or more.

Rated on a scale of 0 or 1: 1 = no, 0 = yes.

†† Rated on a scale of 1 to 5: 5 = excellent, 4 = good, 3 = fair, 2 = poor, 1 = no sleep.

‡‡ Rated on a scale of 1 to 4: 4 = excellent, 3 = good, 2 = fair, 1 = poor.

C. Short-term (5 night) Clinical Efficacy Studies of Quazepam (Q15 mg)

Objective: to assess safety and efficacy of 15 mg quazepam (Q) vs placebo in out-patient insomniacs, as determined by daily patient sleep questionnaires and the investigator's global evaluation at the end of the study.

Design: randomized, double-blind, parallel-groups, consisting of a 3-night single-blind placebo baseline phase and a 5-night double-blind treatment phase.

Measurements: Responses for items 1 to 5 were scored on an increasing scale with highest numbers always indicating most favorable responses, i.e., better sleep. Safety was evaluated using items 6, 7, and 8 on the daily post-sleep questionnaires and the results of PE, ECG and lab tests.

Results:

Three investigators used a common protocol involving 155 outpatients. 's study was terminated after 14 months because only 37 patients had been empaneled and the investigator could not complete the study in a reasonable length of time. No statistically significant results were obtained on the efficacy measures.

, differences between Q15 and placebo on TST were not statistically significant. Q15 induced sleep more quickly than placebo and there were fewer nocturnal awakenings. (Table 4).

Patients in quazepam group dropped out because of treatment failure, and patient on placebo.

differences between Q15 and placebo were not significant in regards to TST and sleep latency. Significant differences in favor of Q15 were observed in 3/4 nights with respect to nocturnal awakenings (Table 4). Daytime somnolence was reported by 7 patients on Q15 and 4 on placebo ($p > .10$).

Two additional investigators used the same short-term protocol comparing Q15 vs placebo (in 's there were no statistically significant differences between Q15 and placebo in regards to efficacy. Patient reported mild nervousness.

Table 3. Mean Values for Items 1 to 5 and Item 9 on the Patients' Postsleep Questionnaires for All Eight Study Nights and for the Overall Treatment Period.*

	Baseline Nights			Treatment Nights					
	1	2	3	4	5	6	7	8	Overall
Sleep Induction Time†									
Quazepam	2.8	3.2	3.4	3.7	3.6	3.5	3.9	3.8	3.7
Placebo	3.3	3.4	3.6	3.7	3.8	3.8	3.2	3.6	3.6
"p"	NSD	NSD	NSD	NSD	NSD	NSD	.10	NSD	NSD
Total Sleep Time§									
Quazepam	2.1	1.9	2.0	3.1	3.0	3.0	3.1	3.0	3.0
Placebo	2.4	2.3	2.6	2.7	2.9	2.9	2.6	2.7	2.8
"p"	NSD	NSD	<.10	NSD	NSD	NSD	NSD	NSD	NSD
Nocturnal Awakenings¶									
Quazepam	3.2	3.2	3.4	4.0	3.9	3.8	4.0	4.1	4.0
Placebo	2.8	2.8	3.2	3.2	3.4	3.6	3.2	3.3	3.4
"p"	NSD	NSD	NSD	<.01	<.10	NSD	<.01	<.01	<.01
Early Morning Awakening#									
Quazepam	0.4	0.4	0.4	0.6	0.7	0.8	0.8	0.8	0.8
Placebo	0.5	0.6	0.5	0.6	0.5	0.7	0.6	0.5	0.6
"p"	NSD	<.10	NSD	NSD	NSD	NSD	<.05	<.01	<.05
Sleep Quality**									
Quazepam	2.7	2.6	2.8	3.6	3.5	3.8	3.8	3.7	3.7
Placebo	2.6	2.7	3.1	3.1	3.1	3.2	3.0	2.8	3.0
"p"	NSD	NSD	NSD	.05	NSD	<.01	<.01	<.01	<.01
Rating of Medication††									
Quazepam	1.7	1.6	1.7	2.6	2.6	2.7	2.8	2.7	2.7
Placebo	1.8	1.8	1.9	2.0	2.2	2.3	2.0	2.0	2.1
"p"	NSD	NSD	NSD	.01	NSD	<.05	<.01	<.01	<.01

* "p" is the probability of no difference between the groups. NSD = no significant difference.

† Rated on a scale of 1 to 5: 5 = 0 to 15 min, 4 = 16 to 30 min, 3 = 31 to 45 min, 2 = 46 to 60 min, 1 = >60 min.

§ Rated on a scale of 1 to 5: 5 = >8 hr, 4 = 7.1 to 8 hr, 3 = 6.1 to 7 hr, 2 = 5.1 to 6 hr, 1 = 5 hr or less.

¶ Rated on a scale of 1 to 5: 5 = no awakenings, 4 = 1, 3 = 2 or 3, 2 = 4 or 5, 1 = 6 or more.

Rated on a scale of 0 or 1: 1 = no, 0 = yes.

** Rated on a scale of 1 to 5: 5 = excellent, 4 = good, 3 = fair, 2 = poor, 1 = no sleep.

†† Rated on a scale of 1 to 4: 4 = excellent, 3 = good, 2 = fair, 1 = poor.

Table 4. Mean Values for Items 1 to 5 and Item 9 on the Patients' Postsleep Questionnaires for All Eight Study Nights and for the Overall Treatment Period.*

	Baseline Nights			Treatment Nights					
	1	2	3	4	5	6	7	8	Overall
Sleep Induction Time†									
Quazepam	2.6	2.9	3.1	3.7	3.5	3.7	3.9	3.7	3.7
Placebo	2.6	2.7	2.8	2.8	2.9	2.9	3.0	3.0	2.9
"p"	NSD	NSD	NSD	<.05	NSD	<.05	<.10	<.10	<.05
Total Sleep Time§									
Quazepam	2.2	2.4	2.8	3.2	3.2	3.3	3.3	3.1	3.2
Placebo	2.3	2.2	2.5	2.7	2.5	2.8	2.8	2.8	2.7
"p"	NSD	NSD	NSD	NSD	<.05	NSD	NSD	NSD	<.05
Nocturnal Awakenings¶									
Quazepam	3.2	3.2	3.4	3.8	3.7	3.9	3.9	3.6	3.8
Placebo	3.1	3.1	3.3	3.4	3.3	3.3	3.4	3.4	3.4
"p"	NSD	NSD	NSD	<.10	<.10	<.05	NSD	NSD	<.05
Early Morning Awakening#									
Quazepam	0.7	0.6	0.6	0.7	0.7	0.7	0.6	0.6	0.7
Placebo	0.5	0.4	0.4	0.6	0.6	0.5	0.6	0.7	0.6
"p"	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD
Sleep Quality**									
Quazepam	2.8	2.9	3.2	3.8	3.7	3.7	3.9	3.4	3.7
Placebo	3.1	2.9	3.1	3.2	3.1	3.3	3.5	3.3	3.3
"p"	NSD	NSD	NSD	.01	<.05	NSD	NSD	NSD	<.05
Rating of Medication††									
Quazepam	1.8	2.2	2.2	2.7	2.7	2.8	2.7	2.6	2.7
Placebo	2.1	1.8	2.1	2.2	2.2	2.1	2.3	2.4	2.2
"p"	NSD	NSD	NSD	<.05	<.05	.01	NSD	NSD	<.01

* "p" is the probability of no difference between the groups. NSD = no significant difference.

† Rated on a scale of 1 to 5: 5 = 0 to 15 min, 4 = 16 to 30 min, 3 = 31 to 45 min, 2 = 46 to 60 min, 1 = >60 min.

§ Rated on a scale of 1 to 5: 5 = >8 hr, 4 = 7.1 to 8 hr, 3 = 6.1 to 7 hr, 2 = 5.1 to 6 hr, 1 = 5 hr or less.

¶ Rated on a scale of 1 to 5: 5 = no awakenings, 4 = 1, 3 = 2 or 3, 2 = 4 or 5, 1 = 6 or more.

Rated on a scale of 0 or 1: 1 = no, 0 = yes.

** Rated on a scale of 1 to 5: 5 = excellent, 4 = good, 3 = fair, 2 = poor, 1 = no sleep.

†† Rated on a scale of 1 to 4: 4 = excellent, 3 = good, 2 = fair, 1 = poor.

differences between Q15 and placebo, with the exception of a marginal difference for TST on the fifth night ($p < .10$). Whereas 7 patients on Q15 reported daytime somnolence, only one did on placebo ($p = .02$). Patient reported abnormal coordination, and patient reported dizziness.

Two short-term studies in inpatients, comparing 4 15 mg vs placebo were carried out under protocol:

did an 8-night (3 nights, single-blind; 5 nights, double-blind), parallel-group study in 56 in-patients withdrawing from chronic alcoholism. The results were not statistically signficant for any of the efficacy items on the 56 patients' sleep questionnaire (Table 2). The patients showed less morning alertness in the Q15 group compared to the placebo group ($p = .05$) (Table 3). Patient on Q15 reported dry mouth and patient #35, a rash on placebo.

Only hospitalized patients entered

This study was <u>terminated</u> prematurely because was unable to enroll the required number of patients in a reasonable length of time. Two patients on Q15 experienced AR: #1 was groggy and #3 was drowsy. Patient #2 on placebo had nightmares on study day 5.

D. <u>Single-dose Studies in Presurgical Patients:</u>

Four studies were done comparing the efficacy and safety of Q 30 mg and 15 mg vs placebo, in hospitalized patients scheduled for elective surgery on the following day. Data were collected primarily from questionnaires and patient interviews.

<u>Objective</u>: to assess hypnotic activity and safety of 30 mg quazepam vs. placebo when administered at bedtime to hospitalized patients scheduled for elective surgery the next morning.

<u>Design</u>: double-blind parallel groups. The patients took either Q30 or placebo at 10:00 p.m. on the night before elective surgery. Patient could request remedication (with safe and effective hypnotic), if not asleep within 2 hrs. In the morning, <u>before</u> any pre-op medications, the investigator administered a patient questionnaire.

Table 2. Mean Values for Items 1 to 5 and Item 9 on the Patients' Postsleep Questionnaires for All Eight Study Nights and for the Overall Treatment Period.*

	Baseline Nights			Treatment Nights					
	1	2	3	4	5	6	7	8	Overall
Sleep Induction Time†									
Quazepam	3.1	3.1	3.2	3.3	3.5	3.2	3.5	3.7	3.4
Placebo	3.1	3.2	3.2	3.6	3.7	3.7	3.7	3.8	3.7
"p"	NSD	NSD	NSD	NSD	NSD	<.10	NSD	NSD	NSD
Total Sleep Time§									
Quazepam	2.8	3.0	2.8	2.9	3.1	3.0	3.2	3.5	3.2
Placebo	2.6	2.9	2.9	3.0	3.2	3.1	3.2	3.2	3.1
"p"	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD
Nocturnal Awakenings¶									
Quazepam	3.6	3.8	3.8	3.6	3.7	3.7	3.8	3.8	3.7
Placebo	3.4	3.7	3.4	3.8	3.6	3.6	3.9	3.7	3.7
"p"	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD
Early Morning Awakening#									
Quazepam	0.7	0.8	0.8	0.9	0.8	0.8	0.8	0.9	0.9
Placebo	0.7	0.9	0.6	0.9	0.8	0.9	0.8	0.9	0.9
"p"	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD
Sleep Quality↔									
Quazepam	3.5	3.7	3.7	3.6	3.8	3.6	3.7	3.7	3.7
Placebo	3.5	3.6	3.6	3.8	3.9	3.7	4.0	3.9	3.8
"p"	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD
Rating of Medication††									
Quazepam	2.7	2.6	2.8	2.6	2.9	2.6	2.8	2.8	2.7
Placebo	2.5	2.5	2.8	2.9	3.0	2.8	3.1	2.8	2.9
"p"	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD

* "p" is the probability of no difference between the groups. NSD = no significant difference.

† Rated on a scale of 1 to 5: 5 = 0 to 15 min, 4 = 16 to 30 min, 3 = 31 to 45 min, 2 = 46 to 60 min, 1 = >60 min.

§ Rated on a scale of 1 to 5: 5 = >8 hr, 4 = 7.1 to 8 hr, 3 = 6.1 to 7 hr, 2 = 5.1 to 6 hr, 1 = 5 hr or less.

¶ Rated on a scale of 1 to 5: 5 = no awakenings, 4 = 1, 3 = 2 or 3, 2 = 4 or 5, 1 = 6 or more.

Rated on a scale of 0 or 1: 1 = no, 0 = yes.

↔ Rated on a scale of 1 to 5: 5 = excellent, 4 = good, 3 = fair, 2 = poor, 1 = no sleep.

†† Rated on a scale of 1 to 4: 4 = excellent, 3 = good, 2 = fair, 1 = poor.

Table 3. Mean Values for Items 6, 7, and 8 on the Patients' Postsleep Questionnaires for All Eight Study Nights and for the Overall Treatment Period.*

	Baseline Nights			Treatment Nights					
	1	2	3	4	5	6	7	8	Overall
Ease of Awakening†									
Quazepam	3.0	3.0	2.8	2.7	2.7	2.7	2.7	2.7	2.7
Placebo	3.0	3.0	3.0	2.9	2.8	2.9	2.9	2.9	2.9
"p"	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD
Morning Alertness§									
Quazepam	2.9	2.8	2.9	2.6	2.7	2.7	2.8	2.7	2.7
Placebo	3.1	2.8	2.8	3.1	2.9	3.1	2.8	2.9	2.9
"p"	NSD	NSD	NSD	<.05	NSD	NSD	NSD	NSD	<.05
Nightmares¶									
Quazepam	1.0	0.9	1.0	1.0	1.0	1.0	1.0	0.9	1.0
Placebo	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
"p"	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD	NSD

* "p" is the probability of no difference between the groups. NSD = no significant difference.

† Rated on a scale of 1 to 4: 4 = very easily, 3 = easily, 2 = with difficulty, 1 = with much difficulty.

§ Rated on a scale of 1 to 4: 4 = wide awake and fully alert, 3 = alert but not at peak, 2 = a little drowsy, 1 = very drowsy.

¶ Rated on a scale of 0 or 1: 1 = no, 0 = yes.

Results:

, 31 patients received Q30, and 30 placebo. 2/31 on Q30 received remedication with a standard hypnotic, and 5 of the remaining 29 took longer than 2 hrs to fall asleep; therefore, treatment was considered a failure in these 7/31 patients on Q30. Treatment was rated a success for 23 patients on Q30. In the placebo group, 10/30 patients received remedication, 6 of the remaining 20 took longer than 2 hrs to fall asleep; treatment was considered a failure in 16/30 patients.

Among the 49 patients who were not remedicated (29 on Q30 and 20 on placebo), the difference in sleep induction time between the 2 groups was not statistically significant (p=.26).

, 33 patients received Q30 and 33 placebo. 13/33 on Q30 needed remedication with a standard hypnotic and were considered treatment failures. The remaining 20 patients fell asleep within 2 hrs and were considered successful. In the placebo group, 15/33 needed remedication and were considered failures. Of the remaining 18 patients, 7 took longer than 2 hrs to fall asleep and were also regarded as failures. Thus, the success rate of Q30 was higher than placebo (61% for Q30 vs 29% placebo).

Among the 38 patients who were not remedicated (20 on Q30 vs 18 placebo), those on quazepam fell asleep more quickly ($p < .01$).

), the same protocol is used, except that the patients are given quazepam 15 mg instead of 30 mg. 7/30 on Q15 needed remedication with a standard hypnotic and were considered as treatment failures. Of the remaining 23 patejnts, 6 took longer than 2 hrs to fall asleep, and were rated as failures. In the placebo group, 11/29 needed remedication and 6/18 took longer than 2 hrs to fall asleep; thus, 17 were regarded as failures. Treatment was successful for 55% on Q15 and 39% on placebo; the difference between the groups was not significant (p=.35).

In this single-dose study, 100 hospitalized patients received quazepam 15 mg, Q30, flunitrazepam 1 mg, F1mg, or placebo orally on the night before elective surgery. There were 20 patients in each group, whose data were evaluable for both efficacy and safety.

Flunitrazepam (Rohypnol) a long-acting (t1/2=10-20 hrs) hypnotic, is not marketed in the U.S. This is another benzodiazepine where there is accumulation of the drug during daily administration.

Comments: Quazepam 30 mg taken on the night before elective surgery by 64 hospitalized patients, was more effective than placebo. However, quazepam 15 mg taken by 30 patients did not achieve significant results.

E. Long-Term (12-week) Clinical Safety Studies:

Eight investigators conducted this 14-week (12 weeks double-blind treatment, followed by 2 weeks single-blind placebo) trial comparing the safety of quazepam 30 mg vs. flurazepam 30 mg, in outpatients with chronic insomnia. Data were collected by the following investigators and subsequently pooled.

Objective: multicentric study to evaluate safety of Q30 vs. flurazepam 30 mg during 12 weeks of treatment and to identify AR that might arise from inappropriate long-term use.

Design: double-blind, randomized, unbalanced-parallel-groups design, with two-thirds of patients receiving Q30. During weeks 1 to 12, patients took assigned treatment; placebo withdrawal in single-blind fashion during weeks 13 and 14 (see Table IV p. 14).

Visit 1: screening: history, PE, ophthalmologic, vital signs, 12-lead ECG, lab tests.
Visit 2: within 10 days for vital signs, brief neurological exam. Medication dispensed for first 2 weeks.
Visits 3,4,5,6 & 7: scheduled to return at end of weeks 2, 4, 8, 12, and 14.
ADR reported at visits 3 to 7, and prn by phone.
Lab tests: monthly at visits 4, 5 and 6.
Repeat eye exam and ECG at visit 6.

Table 1. Schedule of Events in Long-term Safety Study C79-041 With Eight Investigators.

	Visit 1 (Screen)	Visit 2 (Pretreat)	Visit 3 (Week 2)	Visit 4 (Week 4)	Visit 5 (Week 8)	Visit 6* (Week 12)	Visit 7 (Week 14)
Medical History	X	-	-	-	-	-	-
Physical Examination	X	-	-	-	-	X	X
Vital Signs	X	X	X	X	X	X	X
Ophthalmologic Examination	X	-	-	-	-	X	†
Brief Neurologic Examination	X	X	X	X	X	X	X
Electrocardiogram	X	-	-	-	-	X	†
Laboratory Tests	X	-	-	X	X	X	†
Adverse Experience Reports§	-	-	X	X	X	X	X
Acceptance of Treatment:							
Patient Rating	-	-	X	X	X	X	X
Investigator Rating	-	-	X	X	X	X	-
Dispense Medication:							
Active Treatment	-	X	X	X	X	-	-
Placebo	-	-	-	-	-	X	-

* Or any time that a patient discontinued treatment.

† Performed again if results at previous visit were different from results at screening visit in a clinically significant way.

§ Adverse experiences could also be reported any time between visits that was necessary.

SCHERING CORPORATION

PAGE

Results:

381 patients were enrolled by 8 investigators (254 on 630 and 127 on F30). No data exists for 12 patients (lost to follow-up). Thus, there were evaluable data for 369 patients (247 on Q and 122 on F). Table 2 shows the distribution of patients among the 8 investigators.

There were 137 men and 232 women; ages ranged form 18 to 86 yrs with a mean of 48 yrs. Demographic data for 369 patients are presented in Table 3. Table 4 presents insomnia characteristics. Table [illegible] ~~(p. 55)~~ presents distribution of patients by reason and time of dropout.

Table 17 presents the distribution of dropouts by individual investigators and the reason for dropping out (ADR or treatment failure). Seventy patients dropped out because of ADR, 52 (21%) in the quazepam group and 18 (14.7%) in the flurazepam group (p=.147).

Reported ADR:

Of the 247 patients who began treatment with quazepam, 111 (44.9%) dropped out; in the flurazepam group, 42 (34.4%) of the 122 dropped out (p=.054).

No. Patients Reporting Specific ADR During Treatment

	Quazepam (N=247)	Flurazepam (N=122)
Daytime somnolence	85 (34%)	41 (34%)
Hypokinesia	45 (18%)	21 (17%)
Ataxia	35 (14%)	11 (9%)
Confusion	18 (7%)	7 (6%)
Dizziness	14 (6%)	6 (5%)
Depression	13 (5%)	4 (3%)

The incidence of ADR did not differ significantly in the two treatment groups.

Clinically significant events occurred in the following patients:

a male patient (born 4/15/31), having a 20 yr history of asthma, died on 6/5/80. This patient entered the study on 5/5/80, and had completed 12 weeks of quazepam 30 mg. He died during an acute attack of asthma in the first week of placebo withdrawal (wk 13).

Table 2. Disposition of Patients by Investigator and by Treatment Group (O=Cuazepam and F=Flurazepam).

Number of Patients			
Enrolled*		Evaluated	
O	F	O	F
40	20	40	20
41	20	41	20
49	24	43	22
31	16	30	16
17	8	17	7
37	18	37	17
23	12	23	12
16	9	16	8
254	127	247	122
381		369	

Table 3. Summary of Demographic Data.*

	Treatment Group	
	Quazepam	Flurazepam
No. of Patients Treated	247	122
Age in Years		
<21	4	1
21 to 30	39	17
31 to 40	81	35
41 to 50	54	34
51 to 60	66	34
>60	3	1
Sex		
male	94	43
female	153	79
Race		
white	229	114
black	13	6
other	4	1
not specified	1	1

* There was no significant difference between the groups (P>.10).

Table 4. Distribution of Patients in Each Treatment Group by Insomnia Characteristics and History.*

	Quazepam	Flurazepam
Severity of Insomnia		
mild	4	0
moderate	115	50
severe	127	72
Type of Insomnia		
acute	6	2
sporadic	24	10
chronic	216	109
Duration of Insomnia		
<1 year	67	38
1 to 2 years	66	33
>2 to 5 years	41	19
>5 years	71	32
Number of Episodes per Week		
<4	25	11
5	40	17
6	31	17
7	150	76

* There was no significant difference between the groups (P>.10).

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TABLE 3

A LONG-TERM CLINICAL STUDY OF SCH 16134 IN OUTPATIENTS WITH INSOMNIA

Distribution of Patients by Reason and Time of Dropout

Reason for Dropout	Treatment Group	Time in Weeks <2	>2-4	>4-8	>8-12	>12	Total
Adverse Reactions	Quazepam	21	8	14	5	0	48
	Flurazepam	8	5	3	1	0	17
Treatment Failure	Quazepam	1	2	3	2	2	10
	Flurazepam	0	3	0	0	1	4
Other	Quazepam	9	7	14	8	11	49
	Flurazepam	6	4	4	3	4	21
Total	Quazepam	31	17	31	15	13	107
	Flurazepam	14	12	7	4	5	42

Dropouts - Double-Blind Phase (30 mg Quazepam) 12-week study

Investigator	Q	F	Q	F	Q	F	Q	F	Q	F	Q	F	Q	F	Q	F
No. patients	40	20	41	20	43	22	30	16	17	7	37	17	23	12	16	8
Reason:																
Adverse reactions	10	2	16	4	5	5	8	1	2	2	4	1	5	1	2	--
Treatment failure	3	--	2	2	2	--	--	1	--	--	2	--	4	1	1	1
Other	1	--	5	2	14	8	9	3	6	2	5	2	5	5	2	1
Total	14	2	25	8	21	13	17	5	8	4	9	3	14	5	5	2

n	Quazepam 247	Flurazepam 122
Total Dropouts	111 44.9%	42 34.4%
Due to ADR	52 21%	18 14.1%

NDA 18-708
Quazepam

Dropouts - Double-Blind Phase (30 mg Quazepam) 12-week study

Investigator	Q	F	Q	F	Q	F	Q	F	Q	F	Q	F	Q	F	Q	F
No. patients	40	20	41	20	43	22	30	16	17	7	37	17	23	12	16	8
Reason:																
Adverse reactions	10	2	16	4	5	5	8	1	2	2	4	1	5	1	2	--
Treatment failure	3	--	2	2	2	--	--	1	--	--	2	--	4	1	1	1
Other	1	--	5	2	14	8	9	3	6	2	3	2	5	3	2	1
Total	14	2	23	8	21	13	17	5	8	4	9	3	14	5	5	2

n	Quazepam 247	Flurazepam 122
Total Dropouts	111 44.9%	42 34.4%
Due to ADR	52 21%	18 14.7%

NDA 18-708
Quazepam

, a 56-yr old woman had visual hallucinations and severe ataxia, weakness, confusion and disorientation, dizziness, and daytime somnolence after 2 weeks on quazepam 30 mg (5/12-26, 1981). After stopping the medication, all her symptoms abated and no residual effects were noted.

Patient No. 5), a posterior subcapsular cataract (OD) was noted at the post-study ophthalmologic exam, after 12 weeks of quazepam 30 mg, in a 48-yr old male patient. A pre-study eye exam had been reported as normal. found no causal relationship to the medication taken (7/1/81).

Laboratory Tests:

Table // (Vol. 1.59; p. 32) summarizes the results for nine selected tests, including indicators of renal and hepatic function. For each test, the table shows mean pre-treatment and post-treatment values, and the number of patients whose post-treatment values increased or decreased from baseline, stratified by percentage ranges. The results were judged to be clinically signficant in 3 quazepam-treated patients and one flurazepam-treated patient; these results are briefly discussed in Table /2 (Vol. 1.59; p. 34).

a 46-yr old woman with no previous history of liver disease, had increases in SGOT and SGPT at weeks 4 and 8 of treatment with quazepam 30 mg. At the week 6 visit, the patient reported pain and fullness in the RUQ of the abdomen, but the liver was not palpable. Treatment was discontinued at this time. Levels of SGOT and SGPT, along with values for alkaline phosphatase (alk phos) and total bilirubin, are shown below (with normal ranges):

	SGOT (14-40)	SGPT 14-75)	alk phos (12-37)	Total Bili (0.4-1.4)
Screening	25	65	23	0.7
wk 4	52	89	24	0.5
wk 8	61	110	25	0.3
(follow-up)				
after 2 wks	47	38	16	0.4
after 4 wks	79	118	23	0.4
after 7 wks	46	76	22	0.4

states that the patient is well and reports no symptoms. He believes that the increase in SGOT and SGPT was related to quazepam administration, but did not rule out the possibility of another uspecified cause.

ECG and Vital Signs:

No clinically signficant change was observed in the ECG's and vital signs, including heart rate and BP.

Table 11. Summarization of Results From Nine Selected Laboratory Tests: Mean Values Before and After Treatment, and Percentage Changes From Baseline.

Laboratory Tests	Group	Sample Size	Mean Values		Number of Patients With Percent Changes			
			Baseline	After Treatment	Decreases of 25% to 100%	Changes Within 25%	Increases of 25% to 99%	Increases of ≥ 100%
Hemoglobin Level	Q	237	14.7	14.5	1	235	1	0
	F	122	14.5	14.3	0	122	0	0
Hematocrit	Q	237	43.3	42.9	1	236	0	0
	F	122	43.0	42.0	0	122	0	0
Total White Blood Cell Count	Q	237	7.4	7.2	25 (11%)	190 (80%)	22 (9%)	0
	F	122	7.4	7.3	8 (6%)	102 (84%)	11 (9%)	1 (1%)
Blood Urea Nitrogen (BUN)	Q	239	14.0	13.9	30 (13%)	170 (71%)	36 (15%)	3 (1%)
	F	122	14.0	13.9	14 (12%)	92 (75%)	15 (12%)	1 (1%)
Creatinine	Q	238	1.10	1.09	34 (14%)	179 (75%)	20 (9%)	5 (2%)
	F	122	0.99	1.03	15 (12%)	90 (74%)	14 (12%)	3 (2%)
Total Bilirubin	Q	238	0.56	0.50	57 (24%)	117 (49%)	55 (23%)	9 (4%)
	F	122	0.50	0.49	29 (24%)	66 (54%)	23 (19%)	4 (3%)
Alkaline Phosphatase	Q	238	51.7	51.5	19 (8%)	196 (82%)	19 (8%)	4 (2%)
	F	122	56.0	53.7	16 (13%)	96 (79%)	8 (6%)	2 (2%)
Serum Glutamic Oxaloacetic Transaminase (SGOT)	Q	238	20.8	22.5	49 (21%)	133 (56%)	43 (18%)	13 (5%)
	F	120	20.7	19.6	25 (21%)	75 (63%)	16 (13%)	4 (3%)
Serum Glutamic Pyruvic Transaminase (SGPT)	Q	237	22.2	26.8	54 (23%)	115 (49%)	51 (21%)	17 (7%)
	F	120	23.3	22.5	30 (25%)	60 (50%)	25 (21%)	5 (4%)

Table 12. Patients With Clinically Significant Increases From Baseline in Laboratory Tests.

Investigator	Patient	Laboratory Values	Comments
DIAZEPAM GROUP:			
	8 (48 yrs female)	SGOT (14-40) rose from 25 at baseline to 61 at week 4 and 79 at week 8 when treatment was discontinued. SGPT (14-75) rose from 65 to 89 to 110 at the same time. Total bilirubin and alkaline phosphatase were within normal limits.	Investigator and project physician attributed increase in SGOT and SGPT to treatment. See text for more details.
	11 (31 yrs male)	SGOT (5-21) rose from 23 at baseline to 396 at week 10; SGPT (2-28) rose from 16 to 848, and BUN (5-20) rose from 11 to 24 at the same time. Treatment was discontinued. Total bilirubin, alkaline phosphatase, and creatinine were within normal limits.	Liver palpable and tender. Patient admitted self-administering intravenous drugs with nonsterile needle and syringe. Specialized laboratory tests indicated non A, non B type hepatitis. Patient recovered fully after treatment for hepatitis. Not attributed to treatment.
Bremner	4 (39 yrs male)	SGPT (4-25) rose from 35 at baseline to 128 at week 4 and was 108 at week 5 when treatment was discontinued. SGOT (5-26) also rose from 20 at baseline to 60 at week 4 and was 38 at week 5. Alkaline phosphatase (16-70) increased from 65 to 82 at week 4 and was 77 at week 5. Total bilirubin was within normal limits.	Patient has a history of alcoholism and admitted to drinking during the study. Abnormalities not attributed to treatment.
FLURAZEPAM GROUP:			
	19 (48 yrs female)	SGPT (0-46) rose from 26 at baseline to 154 two weeks after treatment was discontinued during week 3 (because of intercurrent illness). SGOT (0-41) increased from 35 to 56 and alkaline phosphatase (30-115) was up from 96 to 168. Total bilirubin was within normal limits.	Patient had been in hospital for two weeks for treatment of arthritis, and had received many unspecified concomitant medications. Abnormalities not attributed to treatment with study drug.

II. Stucies in Geriatric Patients - Quazepam 15 mg

A. Short-term (5 nights) Clinical Efficacy:

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a. Investigator:
(internist)

b. Subjects: 63/70 (7 cropped out during placebo baseline) were evaluated for safety (31 on Q, 32 on P). 57/63 (6 subjects had protocol deviations) were evaluated for efficacy (30 Q, 27P). Ages 60 or over; all subjects had at least 2 complaints (difficulty falling asleep, frequent awakenings, less than 6 hrs TST).

c. Results: for the overall treatment period, only TST, sleep quality, and patient rating of medication were statistically signficant ($p < .01$) in favor of Q15 ~~as~~ over placebo.

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a. Investigator:

b. Subjects: 60 (30 on Q, 30 on P); median age 69

c. Results: Q 15 mg induced sleep more quickly than placebo, maintained sleep longer and produced a better quality of sleep. Daytime somnolence was reported by 12-quazepam treated patients and by 3 on placebo.

---

a. Investigator:

b. Subjects: 60 (31 on Q, 29 on P); median age 71

c. Results: a high placebo response was evident in the patients' global evaluations; only one patient in the placebo group rated therapy poor.

Comments:

Of the 3 short-term (5 nights), double-blind, placebo-controlled studies, comparing the efficacy of quazepam 15 mg vs placebo, in geriatric insomniacs, only the study by) is acceptable; Q15 increased TST significantly better than placebo.

B. Long-term (14-nights) Clinical Safety of Quazepam 15 mg vs F. reference 15 mg

a. Subjects: 101 patients were enrolled by the 3 investigators (51 on Q 15 mg, 50 on F 15 mg). There were 32 men and 69 women; ages ranged from 65-87 yrs.

b. Results: overall incidences of dropouts were not significantly different between the 2 groups ($p > .10$): 5/51 in quazepam group and 4/50 in flurazepam group. One quazepam and 3 flurazepam patients dropped out because of ADRs.

The number of patients reporting treatment related AR are shown in Tables 7 (p. 21) and 8 (p.23).

15 patients reported new AR during (1 wk) placebo withdrawal; 11/15 were recurrences of insomnia. Three quazepam patients reported nausea, anorexia and confusion. Abrupt discontinuation of quazepam was not associated with a withdrawal phenomenon.

Comments:

Three investigators studied 101 geriatric insomniacs in a randomized double-blind clinical trial. At the end of 2 weeks treatment, 73% (37/51) of quazepam patients and 84% (42/50) of flurazepam patients rated treatment as satisfactory ($p=.19$).

C. Effects of Treatment on Memory and Psychomotor Performance in Geriatric Insomniacs (in volume 1.67)

a. Subjects: 48 patients were enrolled by 3 investigators: 16 on Q 15 mg, 17 on F 15 mg, and 15 on placebo. Ages ranged from 64-86 yrs.

b. Results:

Efficacy: effects on sleep latency and ~~and~~ TST (EEG). Both Q15 and F15 were significantly superior to placebo ($p<.05$) with respect to improvement from baseline in TST on first night of treatment. None of the differences in sleep latency were significant.

Psychomotor performance evaluations were carried out at 8:30 a.m. and 2:30 p.m. on the days following each night spent in the sleep lab (screening and days 2, 3, 9 and 16) by means of the following:

Wilkinson Auditory Vigilance Test
4-part Card-Sorting Test
Digit-symbol substitution and copying test

As seen from Table 3 (p. 47) no consistent pattern was observed. In general, there was no deterioration in the quazepam group.

Safety: 23/46 reported one or more ADR: 11 in Q group, 6 in F group and 6 in placebo. Two patients in quazepam group discontinued drug because of ADR:

Patient : 64 yr old woman had severe ataxia and daytime somnolence after night 3.

Patient : 80 yr old man experienced ataxia, diplopia, abnormal coordination and somnolence.

The most frequently reported ADRs were somnolence, fatigue and ataxia. Reports of treatment-related ADR were signficantly ($p < .05$) higher in the quazepam group (6/16) than in either of the other 2 groups (F=2/17; P=3/15).

Comments:

Three investigators ( ) conducted this 16-day (1 day placebo baseline, 7 days double-blind treatment, 7 days placebo washout) trial comparing the efficacy, safety and effects on psychomotor performance of Q 15 mg vs F 15 mg and placebo in 48 geriatric outpatients. Post-treatment observation revealed no evidence of withdrawal in any patient.

III. Special Studies:

Effects of quazepam 15 mg and 30 mg and pentobarbital 50 mg and 150 mg vs placebo on CR function (in vol. 1.30) of healthy adults.

Investigator:

Design:

Single oral doses of quazepam 15 mg and 30 mg, pentobarbital 50 and 150 mg and placebo were administered to 5 healthy males, according to a randomized, DB, Latin square design. Each subject received each of the 5 treatments. One dose was given per week with at least 5-day "washout" intervals. The effects of each drug on respiratory function were measured at baseline and at 1/2, 1, 2, 3, and 4 hrs after drug administration, and on cardiac function at baseline and at 45, 75, and 135 minutes after drug administration.

Results: Quazepam 30 mg produced slight respiratory depression at 3 hrs.

There were no significant drug effects on the slope of the respiratory response curve. This study, in 5 healthy males, suggests that clinically the respiratory and CV effects of quazepam and pentobarbital, at the doses studied, are not significant.

C81-029-01: Secretion of quazepam in breast milk.

Comments:

This study has been reviewed in the detailed review by the Division of Biopharmaceutics (dated 4/26/83; pp 12 and 13). Four healthy, non-pregnant lactating females (26-32 yrs) completed this study. Each subject received a single oral 15 mg quazepam tablet. Breast milk and blood samples were analyzed by gas chromatographic methods, to determine levels of quazepam and its metabolites.

There is excretion of quazepam and its two major active metabolites into breast milk. Through 48 hours following single 15 mg dose administration, total excretion of quazepam, 2-oxoquazepam and N-desalkylflurazepam in breast milk was only 0.11% of the administered quazepam dose.

NDA 18-706 Quazepam

Overall Evaluation:

Quazepam is a hypnotic agent which is related to flurazepam. It is a 1,4-benzodiazepine derivative containing a trifluorethyl, sulfur, and aryl group in the first, second, and fifth positions, respectively (refer to structural formula).

Quazepam has an interesting metabolic and pharmacokinetic profile. Quazepam is rapidly and well absorbed with peak plasma levels reached at approximately 2 hours; 2-oxoquazepam (a major metabolite) was rapidly formed with peak plasma levels occurring at about 4 hours. Both compounds declined in comparable biphasic patterns, with elimination half-lives of approximately 40 hours.

Following oral administration of ^{14}C-quazepam in solution form, the drug is rapidly and extensively absorbed, distributed, metabolized and slowly excreted in the urine and feces over a 5-day period.

The two major active plasma metabolites are 2-oxoquazepam N-desalkylflurazepam. The latter is quazepam's major metabolite at steady state and identical to that seen at steady state with flurazepam. In geriatric patients, the elimination half-life of N-desalkylflurazepam is about twice that of young adults (t1/2=73 hours).

The following studies can be regarded as adequate and well-controlled to support the claims for substantial evidence of relative safety and efficacy for quazepam 15 mg tablets.

A. Objective studies: sleep lab studies which are considered by this reviewer as furnishing substantial evidence of the efficacy of quazepam (15 mg) for short and intermediate-term use:

_____: On the first drug night, Q_{15} increased TST, and on the mean drug night Q_{15} decreased the number of awakenings, decreased wake time after sleep onset and decreased wake time in the last third of the night. On drug withdrawal, there was no evidence of a rebound insomnia.

_____: After Q_{15}, sleep latency decreased from 57.3 minutes to 37.3 minutes, and there was no indication of rebound insomniac during the 15-day withdrawal period.

NDA 18-708 Quazepam

Overall Evaluation:

Quazepam is a hypnotic agent which is related to flurazepam. It is a 1,4-benzodiazepine derivative containing a trifluorethyl, sulfur, and aryl group in the first, second, and fifth positions, respectively (refer to structural formula).

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B. Subjective Studies (until the 1960's, these traditional clinical trials were the only means of evaluating the safety and efficacy of hypnotic drugs.)

Short-term (5 night) quazepam 30 mg: in

. quazepam performed significantly ($p<.05$) better with respect to the efficacy parameters (sleep induction time, TST, nocturnal awakenings).

However, significantly more quazepam patients experienced daytime somnolence and less morning alertness than placebo patients.

Short-term (5 night), quazepam 15 mg: in

, differences between Q_{15} and placebo were not significant in regards to TST. Q_{15} induced sleep more quickly than placebo and there were fewer nocturnal awakenings. In general, Q_{15} did not perform as well (relative to placebo) as Q_{30} with respect to efficacy parameters.

However, Q_{15} showed fewer significant differences with respect to morning alertness and daytime somnolence than Q_{30}.

Short-term (5 night in geriatric patients:
quazepam 15 mg increased TST significantly better than placebo.

Other Studies:

Single-dose studies in presurgical patients:

quazepam 30 mg was administered on the night before elective surgery. These studies yielded consistent results in favor of quazepam 30 mg over placebo with respect to efficacy parameters. Similar favorable results were not achieved by quazepam 15 mg

Effect of Q15 and Q30 vs. placebo on CR function:
, in 5 healthy males suggests that clinically, the respiratory and CV effects of Q_{15} are not significant; however, Q_{30} produced slight respiratory depression at 3 hours. Furthermore, patient a 49 year old male, having a 20 year history of asthma, died on 8/9/80. This patient had completed 12 weeks on Q_{30}. He died during an acute attack of asthma in the first week of placebo withdrawal (week 13). It should be noted that the carry-over effectiveness of Q_{30} after withdrawal may be ascribed to the long half-lives of the drug and its metabolites.

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NDA 18-708 (Quazepam)

Dose-Ranging Studies:

The following two studies were conducted in the sleep lab by investigators with recognized expertise in the conduct of such studies.

This was a DB four-night parallel groups study of placebo vs. quazepam 15, 30, and 45 mg., preceeded by a four night single-blind adaptation and baseline period wherein everyone took placebo,

, and was followed by a two-night single-blind placebo withdrawal period.

24 Ss (17 women and 7 men; ages 31 to 62 years) with insomnia (minimum 3 month history of requiring at least 45 minutes to fall asleep and sleeping less than 6 1/2 hours per night) were studied. Six subjects were randomly assigned to each of 4 treatment groups on nights 5-8: placebo, Q_{15} mg, Q_{30}, and Q_{45} mg.

Sleep was assessed objectively by polysomnographic recordings. Sleep was also assessed subjectively by questionnaires completed by each S each lab morning.

Results:

TST (total sleep time): During the drug period (nights 5-8), TST was almost dose related. Placebo, 15 mg, 30 mg and 45 mg had 376, 400, 419 and 418 minutes sleep, respectively. During the postdrug period (nights 9-10), Q_{30} and Q_{45} had significantly longer sleep times compared with placebo. The higher the dose during the drug period, the longer the sleep during the postdrug period, and also the more the sleep on the first postdrug night.

Sleep latency: During the drug period (nights 5-8), sleep latency was shorter in the Q_{45} ($p<0.05$) and in the Q_{30} ($p<0.08$) than in the placebo group. Also sleep latency was shorter during the drug period than during baseline in Q_{45} ($p<0.01$) and in the Q_{30} ($p=0.05$). Compared to baseline sleep latency, postdrug sleep latency was less in both Q_{45} ($p<0.01$) and Q_{30} ($p=0.05$). Q's effect on sleep latency was not significant at the 15 mg dose.

Nocturnal awakenings: During the drug period (nights 5-8), Q_{30} and Q_{45} significantly reduced the number of nocturnal awakenings; Q_{15} also reduced nocturnal number of awakenings, but not significantly.

Over the four nights (5-8) all three doses of quazepam significantly increased subjective sleep time. During this period, compared with placebo, each Q treated group had significantly shorter subjective sleep latency, and better subjective sleep quality.

Witndrawal effects: In the Q_{30} and Q_{45} groups, the sleep time increase and sleep latency decrease of the drug period persisted during the postdrug nights. This finding suggests that like flurazepam, when Q was administered for several consecutive nights, Q or an active metabolite accumulated in the recipient.

There were no clinically significant differences in the pre and post study PE, EKG's, CBC, SMA-12 or urine tests. Two subjects (#10 and #14) who received Q_{45} mg reported excessive sleepiness each morning following all four nights of drug administration.

Although Q_{15} mg reduction of insomnia was less than at the higher doses (Q_{30} and Q_{45}) the Q_{15} mg dose may be preferable in that there is less likelihood of a dose-related psychomotor performance deficit.

Quazepam was evaluated in doses of 7.5, 15, and 30 mg in a 12-night protocol including four nights of drug trial.

18 insomniacs (more than 45 min. to fall asleep and/or less 6 hrs. TST), ages 22-58 years, were selected from the Sleep Disorders Clinic. Ss were assigned to one of 3 dose groups (6S/group) in a DB fashion.

Results:

Effectiveness of $Q_{7.5}$, Q_{15}, Q_{30} for sleep induction and maintenance

Quazepam	Baseline nights 2-4	Drug nights 5-8	Withdrawal 9-12
7.5 mg			
Sleep latency (min)	39.6	26.8**	28.1**
Wake time after sleep onset	27.1	13.4-	29.6
Total wake time	66.7	40.2**	57.7
Total no. of wakes	13.0	10.5	12.0
15 mg			
Sleep latency (min)	38.4	25.5	34.6
Wake time after sleep onset	34.8	13.6**	31.0
Total wake time	73.2	39.2*	65.7
Total no. of wakes	13.2	09.1	12.1
30 mg			
Sleep latency (min)	44.0	27.9*	19.4*
Wake time after sleep onset	39.4	12.5*	19.1*
Total wake time	83.4	40.5*	38.5*
Total no. of wakes	14.9	10.5*	11.6*

all numbers represent mean values for the 6 Ss
* $p < 0.01$
** $p < 0.05$

Quazepam's effects during both drug use and withdrawal appeared to be dose related: 15 mg induced a greater reduction in wake time after sleep onset than the 7.5 mg dose, and 30 mg induced even greater differences in both wake time after sleep onset and total wake time.

At each dose level, subjective reports of improvement in sleep latency and TST were in agreement with the objective data on quazepam's effectiveness.

Side effects appeared to be dose-related in terms of severity. None of the subjects in the 7.5 mg group reported symptoms of "hangover". In the 15 mg group, 3 Ss (#11, 15R, 17) reported feeling "tired" in the morning after the first drug night, while one subject (#9) had symptoms of moderate morning hangover for the first two mornings after drug administration. In the 30 mg group, moderate morning hangover was evident in 2 Ss following the last three nights of drug administration and into the first withdrawal night (#3 and #13).

NDA 18-708 - (Quazepam)

Conclusions:

1. On 4/18/84, the sponsor informed us that they had re-evaluated NDA 18-708 and had decided to market only the 15 mg dosage. In a dose-response study considered 7.5 and 15 mg as the optimal doses for quazepam. Although Q_{15} did not perform as well (relative to placebo) as the 30 mg dose with respect to the efficacy parameters, there was less morning hangover and daytime sleepiness.

2. The absence of a placebo treatment group, in the long-term (12-week) clinical safety study did not permit a proper assessment of the long-term safety of quazepam 30 mg.

3. Quazepam is contraindicated in patients with COPD, and in patients with established or suspected sleep apnea.

4. During the 15 nights after abrupt withdrawal of quazepam administered for 28 consecutive nights, there was no rebound insomnia (i.e., a marked or statistically significant worsening of sleep above baseline levels). This would be expected in a drug with long half-lives of elimination. In 1973, hypothesized that when bensodiazepines with a long half-life are withdrawn, effects on the BZ receptors are less abrupt because the endogenous BZ-like compounds may be partially restored before the active metabolites of the exogenously administered drugs are completely eliminated.

5. In the short-term (5 nights) study in geriatric insomniacs, Q_{15} increased TST significantly better than placebo. In the long-term (14 nights) studies, abrupt discontinuation of Q_{15} was not associated with a withdrawal phenomenon, during the third week.

6. In the 7-nights study in geriatric insomniacs, at no time was there a significant deterioration in psychomotor performance or memory while on Q_{15}. Post-treatment observation for a week revealed no evidence of withdrawal in any patient.

7. In spite of the shortcomings inherent in sleep lab studies from the limited number of subjects and the high cost per subject night, the more rigorous control of experimental variables contributes to a more precise evaluation of hypnotic drug efficacy than is obtainable with general clinical trials.

NDA 18-708 (Quazepam)

Recommendations:

1. NDA 18-708 for quazepam 15 mg tablets is approvable for the following indication:

   "As a hypnotic for the short term treatment of insomnia characterized by difficulty in falling asleep and/or maintaining sleep." For transient insomnia related to minor situational stress (e.g., hospitalization for elective surgery), a benzodiazepine with a short half-life is preferable.

2. Labeling needs to be revised.

3 SBA to follow.

T. T. Woo, M.D.

Theresa T. Woo, M.D.
(Medical Officer, HFN-120)

cc:
Orig:NDA 18-708 T Hayes 06-03-85
HFN-120
HFN-220
HFN-120/TTWoo/1/8/85
ft/mb/1/8/85
DOC 3008a

Table I - Parameters of nocturnal sleep and wakefulness

		Baseline 2-3-4 X	S.D.	Short Term 5-6-7 X	S.D.	Intermediate Term 16-17-18 X	S.D.	Immediate Withdrawal 20-21-22 X	S.D.	Long Term Withdrawal 23-24-25 X	S.D.
1. Total Recording Time (min)	Q	450.00		450.00		450.00		450.00		450.00	
	T	450.00		450.00		450.00		450.00		450.00	
2. Total Sleep Time (min)	Q	347.59	32.42	383.09	69.87	392.51*	43.26	370.20	61.66	369.81	48.28
	T	363.33	22.60	406.16*	16.72	399.35*	6.73	393.48*	26.09	377.09+□	27.65
3. Sleep Efficiency (%)	Q	77.28	7.24	85.15	15.54	87.22*	9.61	82.33	13.73	83.97*△	11.41
	T	80.75	5.03	90.26*	3.72	88.76*	1.51	85.77	7.76	83.80+	6.15
4. Sleep Latency (min)	Q	41.37	19.63	28.70*	18.67	25.48	17.93	20.24*	12.94	18.45*+	9.68
	T	32.96	38.43	24.40	15.08	27.18	5.87	17.00△	8.47	20.31	10.53
5. Total Nocturnal Wakefulness (min)	Q	95.40	37.17	62.31	70.13	52.70*	42.36	74.63	62.54	70.50△	48.92
	T	80.90	21.03	36.63*	14.94	44.48*	8.35	50.81*	23.61	67.61+□	25.91
6. Wakefulness during 1st 3rd of night (min)	Q	44.18	17.03	27.27*	16.12	25.50*	16.62	18.22*+	13.23	22.03*	9.57
	T	35.85	31.71	21.38	11.39	27.14	3.32	17.64△	4.99	21.61	7.77
7. Wakefulness during 2nd 3rd of night (min)	Q	21.38	18.28	7.55	11.33	7.33*	7.40	8.83	6.84	10.83	9.44
	T	12.96	10.16	3.13	2.52	2.48	1.70	8.44	10.52	12.57+△	8.79
8. Wakefulness during 3rd 3rd of night (min)	Q	32.61	18.02	27.48	45.70	21.87	25.07	47.57△	46.73	35.14	36.86
	T	31.81	19.67	12.11*	9.70	14.85	8.43	24.72	16.37	33.70+	20.75
9. # of awakenings during the night	Q	3.06	0.98	0.72*	0.53	0.83*	0.46	1.22*	0.75	1.39*	1.16
	T	2.11	1.03	0.78*	0.72	0.89*	1.00	1.50	0.86	1.50	0.55

Legend: Average values and standard deviations of the variables listed above are given for each of the 5 assessment periods. Statistical comparisons were done between all 5 assessment periods.
* indicates that the average value is significantly different from the baseline line average ($p<0.05$)
+ indicates that the average value is significantly different from the average of the short term treatment period ($p<0.05$)
△ indicates that the average value is significantly different from the average of the intermediate term treatment period ($p<0.05$)
□ indicates that the average value is significantly different from the average of the immediate withdrawal period ($p<0.05$)

Table I - Parameters of nocturnal sleep and wakefulness

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1. Total Recording Time (min)	Q	450.00		450.00		450.00		450.00		450.00	
	T	450.00		450.00		450.00		450.00		450.00	
2. Total Sleep Time (min)	Q	347.59	32.42	383.09	69.87	392.51*	43.26	370.20	61.66	369.81	48.28
	T	363.33	22.60	406.16*	16.72	399.35*	6.73	393.48*	26.09	377.09+□	27.65
3. Sleep Efficiency (%)	Q	77.28	7.24	85.15	15.54	87.22*	9.61	82.33	13.73	83.97*Δ	11.41
	T	80.75	5.03	90.26*	3.72	88.76*	1.51	85.77	7.76	83.80+	6.15
4. Sleep Latency (min)	Q	41.37	19.63	28.70*	18.67	25.48	17.93	20.24*	12.96	18.45*+	9.68
	T	32.96	38.43	24.40	15.08	27.18	5.87	17.00Δ	8.47	20.31	10.53
5. Total Nocturnal Wakefulness (min)	Q	95.40	37.17	62.31	70.13	52.70*	42.36	74.63	62.54	70.50Δ	48.92
	T	80.90	21.03	36.63*	14.94	44.48*	8.35	50.81*	23.61	47.61+□	25.91
6. Wakefulness during 1st 3rd of night (min)	Q	44.18	17.03	27.27*	16.12	25.50*	16.62	18.22*+	13.23	22.03*	9.57
	T	35.85	31.71	21.38	11.39	27.14	3.32	17.64Δ	4.99	21.61	7.77
7. Wakefulness during 2nd 3rd of night (min)	Q	21.38	18.28	7.55	11.33	7.33*	7.40	8.83	6.84	10.83	9.44
	T	12.96	10.16	3.13	2.52	2.48	1.70	8.44	10.52	12.57+Δ	8.79
8. Wakefulness during 3rd 3rd of night (min)	Q	32.61	18.02	27.48	45.70	21.87	25.07	47.57Δ	46.73	35.14	36.86
	T	31.81	19.67	12.11*	9.70	14.85	8.43	24.72	16.37	33.70+	20.75
9. # of awakenings during the night	Q	3.06	0.98	0.72*	0.53	0.83*	0.46	1.22*	0.75	1.39*	1.16
	T	2.11	1.03	0.78*	0.72	0.89*	1.00	1.50	0.86	1.50	0.55

Legend: Average values and standard deviations of the variables listed above are given for each of the 5 assessment periods. Statistical comparisons were done between all 5 assessment periods.
* indicates that the average value is significantly different from the baseline line average ($p<0.05$)
+ indicates that the average value is significantly different from the average of the short term treatment period ($p<0.05$)
Δ indicates that the average value is significantly different from the average of the intermediate term treatment period ($p<0.05$)
□ indicates that the average value is significantly different from the average of the immediate withdrawal period ($p<0.05$).

Table II - Parameters of nocturnal sleep and wakefulness

		Baseline 2-3-4		Night 5		Night 19		Night 25	
		X	S.D.	X	S.D.	X	S.D.	X	S.D.
1. Total Recording Time (min)	Q	450.00		450.00		450.00		450.00	
	T	450.00		450.00		450.00		450.00	
2. Total Sleep Time (min)	Q	347.59	32.42	377.16	68.53	383.83▽	73.04	341.94	83.18
	T	363.33	22.60	415.55	10.51	213.39	87.29	368.89	24.99
3. Sleep Efficiency (%)	Q	77.28	7.24	83.84	14.36	85.29▽	16.23	81.36	19.40
	T	80.75	5.03	92.34	2.33	47.41	19.40	81.97	5.56
4. Sleep Latency (min)	Q	41.37	19.63	31.77	21.17	27.39	31.25	15.65	11.95
	T	32.96	38.43	22.27▽	17.22	85.00	66.50	17.38	9.06
5. Total Nocturnal Wakefulness (min)	Q	95.40	37.17	68.50	65.33	61.16	73.52	87.27	81.93
	T	80.90	21.03	26.50	10.01	235.16▽	88.27	75.83	24.23
6. Wakefulness during 1st 3rd of night (min)	Q	44.18	17.03	35.61	20.51	25.16	31.17	18.83	9.69
	T	35.85	31.71	15.83	11.04	96.16▽	37.09	24.39	15.40
7. Wakefulness during 2nd 3rd of night (min)	Q	21.38	18.28	4.38	2.87	4.61	5.16	16.89	22.92
	T	12.96	10.16	1.61	1.47	58.05	58.48	5.77	6.43
8. Wakefulness during 3rd 3rd of night (min)	Q	32.61	18.02	28.50	49.57	31.38	41.98	44.11	59.08
	T	31.81	19.67	9.05	6.80	80.94	47.27	45.66	34.21
9. # of awakenings during the night	Q	3.06	0.98	1.33	1.03	1.17	0.75	1.00	1.10
	T	2.11	1.03	0.67	0.82	3.33	3.08	1.17	0.75

Legend: For the variables listed above, average values and standard deviations are given f - the baseline period and nights 5, 19 and 25 individually. Statistical comparisons for the same night were done between the two drugs tested. ▽ indicates that the average value is significantly different ($p<0.05$) from the average value of the other drug, when compared for the same night.

Table III - Parameters of nocturnal sleep and wakefulness

		Baseline 2-3-4	Intermediate Term 16-17-18		Night 19	
		X	X	Efficacy from baseline	X	Efficacy from baseline
1. Total Sleep Time (min)	Q	347.59	392.51*	+12.92%	383.83 ▽	+ 10.42%
	T	363.33	399.35*	+ 9.91%	213.39	- 41.26%
2. Sleep Efficiency (%)	Q	77.28	87.22*	+12.86%	85.29 ▽	+ 10.36%
	T	80.75	88.76*	+ 9.91%	47.41	- 41.28%
3. Sleep Latency (min)	Q	41.37	25.48	-38.40%	27.39	- 33.87%
	T	32.96	27.18	-17.53%	85.00	+157.88%
4. Total Nocturnal Wakefulness (min)	Q	95.40	52.70*	-44.75%	61.16	- 35.89%
	T	80.90	44.48*	-45.01%	235.16 ▽	+190.67%

Legend:

* indicates that the average value is significantly different from the baseline average ($p < 0.05$)
▽ indicates that the average value is significantly different ($p < 0.05$) from the average value of the other drug, when compared for the same night.

Table VI - Total sleep time on individual study nights

Night			Total Sleep Time (minutes) Quazepam X	Quazepam S.D.	Triazolam X	Triazolam S.D.
		PLACEBO				
	1		324.38	69.45	359.89	22.47
	2		339.22	55.03	367.00	29.51
	3		344.99	32.74	356.72	32.13
	4		358.55	43.27	366.27	38.48
	5		377.16	64.53	415.55	10.51
	6		394.94	43.31	398.50	24.47
	7		377.16	104.52	404.44	20.85
Home Nights	8 - 14	DRUG				
	15		363.33	80.83	386.44	19.01
	16		358.38	44.35	400.27	10.88
	17		389.50	50.82	398.05	18.02
	18		389.67	47.38	399.72	13.28
	19	PLACEBO	383.83▽	73.04	213.39	87.29
	20		361.22	72.81	395.22	19.31
	21		380.00	48.41	407.67	22.32
	22		369.39	82.34	377.55	58.70
	23		380.44	51.34	379.16	52.19
	24		387.05	52.67	383.22	52.93
	25		341.94	81.18	368.89	24.99

Legend:

▽ Indicates that the average value is significantly different ($p<0.05$) from the aver value of the other drug when compared for the same night.

PHARM. REVIEW

Review and Evaluation of the Pharmacology and Toxicology Data and Relevant Clinical Data of NDA 18-705
Drug Abuse Staff Consulting Review

Sponsor: Schering Corporation
60 Orange Street
Bloomfield, New Jersey 07003

Drug: quazepam

(7-chloro-5-(O-fluorophenyl)-1,3-dihydro-1-(2,2,2-trifluoroethyl(-2H-1,4-benzo-diazepine)-2-5 thione.

Category: Benzodiazepine hypnotic agent

Background

Quazepam is a substituted 1,4 benzodiazepine agent which is seeking approval as a hypnotic agent. The clinical dosage form will be tablets of 15 and 30 mg strength. The indication is for the treatment of all types of insomnia, characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings. Quazepam is claimed to be effective in patients with recurring insomnia or poor sleep habits, acute or chronic medical situations requiring restful sleep, insomnia in geriatrics, and insomniac situations where fast onset is desirable. The sponsor believes that quazepam has a unique profile of effects and lacks substantive abuse liability. The sponsor's data and arguments, which are summarized in an April 14, 1983 submission for the Drug Abuse Advisory Committee meeting of April 28 and 29 of 1983, will be reviewed below. The sponsor's premise is that quazepam selectively stimulates a subset of benzodiazepine receptors which are responsible for sedation and sleep, but not a potential for abuse. The sponsor also claims that preclinical evaluations have demonstrated a long duration of action, less potential for ataxia, paradoxical excitation, and (less) tolerance than other benzodiazepines such as flurazepam.

On page 11 of the April 14, 1983 submission the sponsor has profiled the relative effects of quazepam and flurazepam in three different indications of sedative hypnotic potential in mice in Table 1. In general quazepam appears to be equipotent or slightly more potent than flurazepam in the test of hypnotic activity in mice. It should be noted that the LD_{50} of quazepam by mouth is greater than 5,000 mg/kg, suggesting an excellent therapeutic index. In terms of relative toxicity, quazepam is less toxic by mouth than chlordiazepoxide, diazepam, and temazepam. Flurazepam and oxazepam appear to be equitoxic to quazepam.

The squirrel monkey was the species chosen to study hypnotic effects of quazepam. Quazepam was approximately twice as potent in producing eyelid closure (a measure of sedation and hypnosis) than flurazepam. Flurazepam and quazepam were equipotent in producing ataxia. Thus, quazepam appears to produce less ataxia at equihypnotic doses.

Quazepam was also evaluated in the freely moving cat. Quazepam and flurazepam were equipotent in producing the behavioral effects (sedation and drowsiness), but flurazepam appeared to be more potent in terms of muscle relaxation and far more potent with respect to producing ataxia. Thus, in the cat, a dissociation between the sedative effect and the ataxic effect of quazepam has been demonstrated, whereas with flurazepam one would expect a greater degree of overlap. Further escalations of dose also revealed differences between flurazepam and quazepam. Quazepam produced increased drowsiness and sedation in all five cats tested up to 1,000 mg/kg, p.o. Flurazepam, on the other hand, produced stimulant effects at higher doses and all cats died at doses ranging from 250 to 600 mg/kg, p.o. Acute lethality data in the cat suggest that quazepam has less acute toxicity than flurazepam. Given that quazepam and flurazepm are approximately equipotent with respect to sedation and hypnosis in the cat, this suggests that quazepam has a good margin of safety in the cat.

Other data obtained in both mice and cats appears to substantiate the differences observed betwen quazepam and flurazepm with respect to "paradoxical" excitation. In the mouse, quazepam produces a dose-related suppression of locomotor activity, whereas flurazepam incrases locomotor activity in doses up to 5 mg/kg. EEG studies in immobilized cats also support the difference with respect to paradoxical excitation. Following quazepam administration, the EEG is consistent with sedation, showing slow wave and spindle activity, whereas the EEG following quazepam administration snows beta activity, suggesting a stimulatory component to the action of flurazepam.

Quazepam was tested for reinforcing properties in an intragastric self-administration model in the rhesus monkey. These data are presented in Table 5 on page 20 of the sponsor's submission. The data show that only 2 of 4 monkeys initiated self-administration at the unit dose of 0.25 mg/kg. When higher doses, 1 to 4 mg/kg were tested, the 2 monkeys who did not self-administer at the 0.25 dose also failed to administer at the higher doses. The 2 monkeys who self-administered at the 0.25 mg/kg dose administered less quazepam at the unit doses of 1 and 4 mg/kg. Animals received 2 weeks of programmed administration of the drug at 1 mg/kg every 4 hours daily for 2 weeks. Even following this manipulation, the self-administration of doses in the 0.25 to 4 mg/kg range was marginal. These results may be best appreciated when compared to a standard drug in this intragastric self-administration paradigm. Yanagita and Cato reported on the intragastric self-administration of diazepam in the monkey. (Presented at the CPDD meeting in Toronto in 1982). A dose of diazepam 0.25 mg/kg increased rate of responding (over

saline control) in 2 of 4 monkeys. At a dose of 1 mg/kg, responding was maintained above the original vehicle level in only 1 of 4 subjects and only this subject retained relatively high levels of drug intake when the dose was again set at 0.25 and, subsequently, reset to 1 mg/kg. When a vehicle probe was inserted for three days, the animal showed rates of responding higher than originally maintained by vehicle in 2 of 4 subjects. Further unit doses of 1 and 2 mg/kg of diazepam did not increase intake appreciably above vehicle level. A final return to a vehicle probe for 1 one week generally resulted in levels of responding that were comparable to the second determination of vehicle levels and greater than the levels of vehicle maintained initially. Although the results of this study indicate intragastric diazepam was self-administered by the rhesus monkey, the effect is weak-to-modest at best. Moreover, the self-administration of diazepam and quazepam show few, if any, relevant differences in the intragastric self-administration model. Furthermore, the results obtained in the intragastric self-administration model in the rhesus monkeys are probably representative of benzodiazepine self-administration paradigms in general. Griffiths and Ator (1981) reported that benzodiazepine self-administration studies show these drugs to be considered moderately reinforcing. These authors concluded that benzodiazepines as a class are more efficacious as reinforcers than chlorpromazine, imipramine, haloperidol or Perphenazine, but were clearly less efficacious than amobarbital, secobarbital, alcohol, or cocaine. (Griffiths, R.R. and Ator, N.A. In Benzodiazepines, S.I. Szara, and J.P. Ludford (Eds.), NIDA Research Monograph 33, U.S. Government Printing Office, Washington, D.C., page 22-36, 1981.

The sponsor had indicated that the self-administration profile of quazepam is similar to halazepam. Thereafter the sponsor discusses the differential selectivity of both quazepam and halazepam for BZ_1 receptors. It has been reported by Jaffe, et al, (1983) that halazepam is substantially less euphoric than diazepam. The sponsor then develops an analogous argument that quazepam should have substantially less psychological dependence capacity. However, in the monkey, the self-administration profile of quazepam is also similar to diazepam (vide supra). Thus, the selective or relatively selective affinity for one receptor subtype over another has not been correlated with a reinforcement or lack of reinforcement effect. Thus, the sponsor's analogous reasoning is faulty and the sponsor has not demonstrated any less liability for psychological dependence than diazepam.

Tables 6, 7 and 8 (of the sponsor submission) illustrate the preference of halazepam and quazepam for the "BZ_1 receptor." The "BZ_1" receptor density is highest in the cerebellum and the "BZ_2" type receptor occurs with greater prevalence in the hippocampus. Although I am in agreement with the sponsor's analysis that quazepam has preferential affinity for the "BZ_1" receptor, it is only speculation as to whether this confers unique properties onto quazepam; i.e., a lack of abuse.

The next section of the sponsor's report deals with issues of tolerance and physical dependence. The sponsor has demonstrated in Figure 5 that quazepam pretreated mice do not develop tolerance to the anticonvulsant effect of quazepam, whereas flurazepam-treated mice demonstrate tolerance. It should be noted that tolerance development to a specific effect does not imply that a global tolerance to all drug effects are occurring. It should be appreciated that the lack of tolerance to one effect does not imply that tolerance can not develop to another effect. It should also be noted that tolerance is neither a necessary nor a sufficient condition for physical dependence to occur. The role of tolerance in the maintenance of drug-seeking behavior in drug-abusing populations is severalfold:

1. It shortens the duration of action and decreases potency of drugs, necessitating an increased amount of drug and shorter inter-drug ingestion or injection intervals; (This has implications in terms of both operant and classical conditioning effects).

2. It can magnify the appetitive effects of a drug due to tolerance development to aversive effects (e.g., vomiting);

3. It may confer additional safety to a drug in a drug-abusing population; that is, there may be fewer overdoses in an abusing population per dose as opposed to a drug-naive population.

The physiologic dependence capacity of quazepam has been studied in rhesus and squirrel monkeys. In rhesus monkeys, increasing doses of quazepam were administered to 5 monkeys over a five-week period. Abrupt withdrawal was performed at the beginning of the fifth week. Mild withdrawal signs were seen in 3 of 5 monkeys (apprehension, hyperirritability, mild tremor, anorexia, and piloerection) and intermediate withdrawal signs were seen in 2 of 5 monkeys (aggravated tremor, muscle rigidity, impaired motor activity, retching or vomiting, or weight loss of 10%). It should be noted that the aforementioned signs designate the differentiation of mild and intermediate withdrawal. They are not necessarily observed in every monkey. Quazepam was again administered for four weeks, the highest dose being 64 mg/kg/day. At the beginning of the 10th week, a second withdrawal period was initiated. There was a slight increase in withdrawal severity with 3 of 5 having intermediate withdrawal signs and 2 of 5 monkeys having mild withdrawal signs.

Quazepam was tested for substitution capacity in a barbital-dependent rhesus monkey model. Quazepam produced incomplete suppression of withdrawal at 4 mgs and complete suppression of withdrawal in 2 to 4 monkeys at 8 and 16 mg/kg. For comparison, flurazepam at 16 mg/kg also produced complete suppression in 2 of 4 monkeys.

The physical dependence capacity of quazepam was also studied in squirrel monkeys. Quazepam doses of 2, 5 or 50 mg/kg was administered for 52 weeks. An additional group received diazepam, 50 mg/kg. The highest doses of quazepam and diazepam are approximately 83 and 63 times the usual therapeutic

daily doses, respectively, (based on mg/kg comparisons between man and monkey). Dose and drug-related sedation, somnolence, ataxia and tremors were observed. The frequency was greatest during the first three weeks of dosing. During the first week of the study, several high-dose quazepam- and diazepam-treated monkeys were unable to move without falling. Following the last doses of quazepam and diazepam, animals were observed for withdrawal signs. Ataxia, emesis, tremors, and convulsions occurred within 3 days of cessation of dosing. Convulsions lasted a few minutes, and were followed by either complete recovery or death. One monkey found convulsing was given diazepam and appeared normal 20 minutes later. Three days later the animal convulsed and died several days later.

The dose-time relationships and comparative physical dependence capacity of benzodiazepines are poorly understood. The data in the rhesus monkey on quazepam are not comparable to other data derived even in the same laboratory. For comparison purposes, the animals would have to have been put on a chronic equivalent dosing regimen similar to that described by Boisse and Okamoto, 1978 (see Boisse, N.R. and Okamoto, M., J. Pharmacol. Exp. Ther., Vol. 204: 497, 1978). To my knowledge, the only comparative benzodiazepine physical dependence study on record is the Schering study with quazepam and diazepam in the squirrel monkey. Thus, there is not enough background information to judge the validity of this model in terms of the relevance to physical dependence in the human. It should be noted that this study utilized high doses of quazepam and diazepam administered for a long period (52 weeks). The severe convulsions and lethality which occurred in both the quazepam and diazepam groups have not been observed in other models of benzodiazepine physical dependence. It should be noted that convulsions have been reported in patients withdrawing from benzodiazepines. However, no lethalities have been reported for benzodiazepine withdrawal syndromes.

The sponsor has added a section which overviews the clinical studies with quazepam. Table 14 gives a distribution of adverse reactions as a function of treatment. It should be noted that although the quazepam side effect incidence appears to be less than for flurazepam, the dose levels are not mentioned. Thus, it may be that the combined 15 and 30 mg dosage data on quazepam may have lesser side effects than that seen with flurazepam. I have one other comment about the clinical studies. Table 21 illustrates that in studies of between 4 and 18 nights there was essentially no REM rebound during the post-drug period. This would be expected given a drug with a long half-life of elimination.

The sponsor has also a provided a summary of the metabolic and pharmacokinetic data on quazepam. Of particular interest is the fact that quazepam is rapidly absorbed with a peak plasma concentration occuring between 1 and 2 hours. The terminal half-life of quazepam and 2-oxoquazepam are fairly long, being 39.3 and 40.2 hours as reported in Figure 1, respectively. Additionally, N-desalkylflurazepam, an active metabolite with a terminal elimination

half-life of 69.5 hours has also been noted. The pharmacokinetics of quazepam may bear on the abuse potential of the substance. It has been suggested that the reinforcing properties of rapidly absorbed benzodiazepines may increase their abusability, in that person's using these drugs for pleasure-seeking may select those which are rapidly absorbed. (See Stitzer, et al, Drug and Alcohol Dependence, Vol. 8., page 189, 1981; Griffiths and Ator, 1981). Jasinski, et al (1981) reported that 10, 20 and 40 mg of diazepam produced pentobarbital like euphoria with a time course similar to pentobarbital. See Jasinski, D.R., Haertzen, J.E., Henningfield, R.E., Johnson, R.E., Makhzoumi, H.M., Miasato, K. reported to Committee on Problems of Drug Dependence, 1981). Griffiths, et al, 1980 administered diazepam and pentobarbital to sedative hypnotic abusers over a wider dose range. The results suggest a flatter dose response for diazepam as only modest elevations of subject liking were recorded for diazepam, and pentobarbital was consistently preferred. The results also suggest that euphoria inhibiting effects of residual benzodiazepine levels may affect liking scores and drug preference in a chronic administration paradigm. Diazepam and desmethyldiazepam have fairly long elimination half-lives, thus possibly limiting the amount of receptor stimulation seen in chronic dosing situations. This could reduce the amount of CNS effect perceived and result in a diminution of the liking score. Quazepam has not been tested in a self-administration paradigm in sedative-hypnotic abusers. It would be my prediction that quazepam would have a liking score similar to pentobarbital in a Jasinski model, and similar to diazepam in a Griffiths model. At any rate, the sponsor could test for differences in liking scores in either or both models and possibly demonstrate whether there really is a difference in the magnitude or time course of the liking scores which could translate to a difference in abuse potential.

The dependence potential of quazepam has to be viewed from at least two perspectives. The first perspective is whether or not a patient population would become dependent on quazepam. At this time data do not exist to answer the question. Quazepam should be administered to a group of insomniacs who are allowed to freely dose for a given period of time. The drug should be compared to a known standard and possibly also to placebo. The amount of time that subjects stay on quazepam as opposed to the active control and placebo and the preference of quazepam to the other two drugs might give a better indication of the drug's abuse potential in a chronic patient population. The second concern would be a concern of actual physical dependence in both a patient population and a drug abusing population. Obviously, one might be more concerned with a drug abusing population since they would likely abuse the drug at higher doses. The dose-time relationships for physical dependence attainment for any benzodiazepine have not been worked out. Thus, I can only speculate as to whether or not quazepam would produce physical dependence in a patient population. To date, studies suggest that clinical doses, i.e. up to 30 mg a night for 4 weeks, do not produce a significant withdrawal syndrome. However, therapeutic dosing for longer than four months or more or increases in dose might increase the incidence of withdrawal reactions. It would seem

prudent to allow that gradual tapering of the dose should occur to minimize the possibility of withdrawal emergence.

Conclusions:

The sponsor has not demonstrated that quazepam is signficantly different from other benzodiazepines with respect to abuse potential. Available behavioral and biochemical data in animals suggest that quazepam may selectively stimulate a benzodiazepine type I receptor. However, whether this will correlate with a reduced abuse potential is unknown at this time. The physical dependence properties of quazepam cannot be compared to any known benzodiazepine or other sedative-hypnotic. However, it can be stated with some degree of certainty that physical dependence can be produced with high doses given over a fairly long period of time. Additional studies could evaluate the dose-time relationships involved in determining the dependence potential of quazepam.

The pharmacokinetic data demonstrate that quazepam is rapidly absorbed and has active metabolites with long half-lives. Assuming a correlation between rate of drug rise in plasma and CNS depression, these data suggest that quazepam would produce rapid sedation. This property indicates a potential for abuse similar to other Schedule IV benzodiazepines. The long half-lives of quazepam and its metabolites might decrease dosing in a chronic situation; such an observation has been made by Griffith, et al., 1980 in a population of sedative-hypnotic abusers who were chronically administering diazepam. Methodologies exist to test both the single and chronic subjective effects of quazepam vis-a-vis halazepam and diazepam. I would recommend that such a study be done if the sponsor wants to demonstrate a difference in abuse potential between diazepam and quazepam.

Recommendation:

Quazepam should be placed in Schedule IV of the Controlled Substances Act if and when quazepam is approved for marketing.

Frank J. Vocci Jr., Ph.D.
Frank J. Vocci, Jr., Ph.D.

cc:
Orig. NDA
HFN-220
HFN-120
HFN-123/FVocci/4/21/83
Edit:FVocci/4/26;4/28/83
FT/dcm:4/22/83/ica:4/26/83
RD/dcm/4/27;4/28/83
DOC# 5837B

Robert Hollenbeck, Ph.D.
June 3, 1985

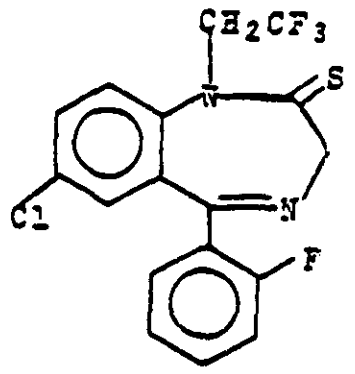
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
ORIGINAL SUMMARY NDA 18-708

Sponsor: Schering Corporation
Bloomfield, New Jersey

Drug: Quazepam

Category: hypnotic

Chemical Structure:-



Chemical Names:

1) 7-Chloro-5-(2-fluorophenyl)-1,3-dihydro-1-(2,2,2-trifluorophenyl)-2H-1,4-benzodiazepine-2-thione

2) 7-Chloro-5-(o-fluorophenyl)-1,3-dihydro-1-(2,2,2-trifluorophenyl)-2H-1,4-benzodiazepine-2-thione

Drug Code Number: SCH 16134

Trade Name: not yet available

Formulation: Tablets of 15 and 30 mg Quazepam

Proposed Clinical Indication:

For the treatment of all types of insomia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings. Quazepam is claimed to be effective in patients with recurring insomnia or poor sleep habits, acute or chronic medical situations requiring restful sleep, insomnia in geriatrics, and insomniac situations where fast onset is desirable.

Preclinical Studies and Testing Laboratories:

Except for a mouse reproduction study which was performed by Huntingdon Research Centre, U.K., the testing of quazepam was conducted at Schering Corporation, Department of Pathology and Toxicology. Tables showing types of studies performed, results obtained and descriptive material, were prepared by the sponsor and have been included in several parts of this review.

Relationship to Other Chemically and Pharmacologically Related Drugs:

Quazepam is a hypnotic agent which is related to flurazepam and diazepam. It is a 1,4-benzodiazepine derivative containing a trifluoroethyl, sulfur, and aryl group in the first, second, and fifth positions, respectively.

QUAZEPAM

Table of Contents

Table 1. – TOXICOLOGY AND PATHOLOGY PRECLINICAL INVESTIGATIONS OF QUAZEPAM

Species	# Males	# Females	# Animals/ Group	Study Design	Study Duration	Quazepam Daily Dosage	Route of Administration	Dosage Form
Mouse	20	20	20	Acute	2 wks (single administration)	0,5000 mg/kg	Oral (esophageal intubation)	suspension
	70	60	10[a]	Acute	2 wks (single administration)	0,525,603,695, 795,845,893,915, 945,1000,1050, 1060 mg/kg	Intraperitoneal Injection	suspension
	80	80	40	Subacute	13 wks	0,5,25,100[b] mg/kg	Oral (esophageal intubation)	suspension
	40	40	40	Subacute	13 wks	0,50 mg/kg	Oral (esophageal intubation)	suspension
	75	150	45	Segment I	F_0: 16 wks F_1: 16 wks	0,6,18,54 mg/kg 54 mg/kg-diazepam	Oral (gavage)	suspension
	–	125	25	Segment II	3 wks	0,3,20,120 mg/kg 160 mg/kg-diazepam	Oral (esophageal intubation)	suspension
	–	125	25	Segment III	6 wks	0,3,9,18 mg/kg 18 mg/kg-diazepam	Oral (esophageal intubation)	suspension
	–	100	25	Segment III	6 wks	0,9,18 mg/kg 18 mg/kg-diazepam	Oral (esophageal intubation)	suspension
	240	240	40[c]	Oncogenicity	79-91 wks	0,30,60,120 mg/kg	Oral (diet)	bulk (powder)

[a] – 20 vehicle control mice/group
[b] – Treatment terminated at Week 3
[c] – 240 control mice/group

Table I. - TOXICOLOGY AND PATHOLOGY PRECLINICAL INVESTIGATIONS OF QUAZEPAM

Species	# Males	# Females	# Animals/ Group	Study Design	Study Duration	Quazepam Daily Dosage	Route of Administration	Dosage Form
Rat	20	20	20	Acute	2 wks (single administration)	0,5000 mg/kg	Oral (esophageal intubation)	suspension
	50	60	20	Acute	2 wks (single administration)	0,2000,2520, 3160,3980, 5000 mg/kg	Intraperitoneal Injection	suspension
	70	-	10	Acute	2 wks (single administration)	0,1250, 2500, 5000 mg/kg 1250,2500, 5000 mg/kg-SOI 15725	Oral (esophageal intubation)	suspension
	90	70	8 to 12	Acute	2 wks (single administration)	0, 1000 mg/kg	Oral (gavage)	suspension
	20	20	10	Subacute	3 wks	0,50,100, 200 mg/kg	Oral (diet)	bulk (powder)
	-	110	25[d]	Segment II	3 wks	0,25,50, 100 mg/kg	Oral (esophageal intubation)	suspension
Hamster	40	40	16[e]	Subacute (Pilot)	5 wks	0,125,250, 500 mg/kg	Oral (diet)	bulk (powder)
	216	216	72[f]	Chronic	52 wks	0,3,20,120 mg/kg 120 mg/kg-diazepam	Oral (diet)	bulk (powder)
	336	336	112[g]	Carcinogenicity	57-79 wks	0,3,20,120 mg/kg 120 mg/kg-diazepam	Oral (diet)	bulk (powder)

[d] - 35 vehicle control females/group
[e] - 32 control hamsters/group
[f] - 144 control hamsters/group
[g] - 224 control hamsters/group

Table I. - TOXICOLOGY AND PATHOLOGY PRECLINICAL INVESTIGATIONS OF QUAZEPAM (Cont'd.)

Species	# Males	# Females	# Animals/ Group	Study Design	Study Duration	Quazepam Daily Dosage	Route of Administration	Dosage Form
Rabbit	-	58	14[f]	Segment II	4 wks	0,10,20,40 mg/kg	Oral (esophageal intubation	suspension
Dog	1	1	2	Acute	3 wks	1000 mg/kg	Oral	capsule (powder)
	1	2	2[h]	Dose Range	6 wks	0,50,100,200, 400,800,1600 mg/kg	Oral	capsule (powder)
Monkey	13	15	6[i]	Subacute	13 wks[i]	0,2,10,50,50[i] mg/kg	Oral (gavage)	suspension
	25	25	10	Chronic	56 wks	0,2,10,50 mg/kg 50 mg/kg-diazepam	Oral (gavage)	suspension
Cat	-	10	5	Dose Range	approx. [g] up to 7 wks	0.1-1000 mg/kg 0.1-600 mg/kg-flurazepam	Oral	capsule (powder)

f - 16 vehicle control rabbits/group
g - 4 weeks post-treatment included
h - 1 control female dog
i - An additional group of four high-dose monkeys were evaluated for post-treatment effects for 24 days following a 13-week dosing period.

Table I. - TOXICOLOGY AND PATHOLOGY PRECLINICAL INVESTIGATIONS OF QUAZEPAM (Cont'd.)

Species	# Males	# Females	# Animals/ Group	Study Design	Study Duration	Quazepam Daily Dosage	Route of Administration	Dosage Form
Rabbit	-	58	14[f]	Segment II	4 wks	0,10,20,40 mg/kg	Oral (esophageal intubation	suspension
Dog	1	1	2	Acute	3 wks	1000 mg/kg	Oral	capsule (powder)
	1	2	2[h]	Dose Range	6 wks	0,50,100,200, 400,800,1600 mg/kg	Oral	capsule (powder)
Monkey	13	15	6[i]	Subacute	13 wks[i]	0,2,10,50,50[i] mg/kg	Oral (gavage)	suspension
	25	25	10	Chronic	56 wks	0,2,10,50 mg/kg 50 mg/kg-diazepam	Oral (gavage)	suspension
Cat	-	10	5	Dose Range	approx. 9 up to 7 wks	0.1-1000 mg/kg 0.1-600 mg/kg-flurazepam	Oral	capsule (powder)

f - 16 vehicle control rabbits/group
g - 4 weeks post-treatment included
h - 1 control female dog
i - An additional group of four high-dose monkeys were evaluated for post-treatment effects for 28 days following a 13-week dosing period.

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Pharmacology Synopsis

Test	Drug	Route	ED_{50} (mg/kg)
(1) potentiation of hexobarbital-induced sleeping time in mice	quazepam	p.o.	2.7
	flurazepam	p.o.	3.9
	diazepam	p.o.	1.0
(2) antagonism of electroshock (13mA, 60Hz) induced convulsions in mice	quazepam	p.o.	0.9
	flurazepam	p.o.	1.6
	phenobarbital	p.o.	5.6
(3) antagonism of isolation-induced agression in mice	quazepam	i.p.	10.7
	flurazepam	i.p.	40.0
	diazepam	i.p.	8.7
(4) antagonism of footshock-induced fighting-in mice (0.5mA)	quazepam	p.o.	1.5
	flurazepam	p.o.	1.5
	diazepam	p.o.	1.5
(5) antagonism of metrazol-induced seizures in mice	quazepam	p.o.	0.3
	flurazepam	p.o.	1.7
	diazepam	p.o.	0.3

Quazepam was found to be twice as potent as flurazepam and half as potent as lorazepam as a hypnotic as measured using the eye-closure test in monkeys. Some of the above-mentioned tests are used to evaluate the drugs potential as a tranquilizer or an anticonvulsant even though this compound is to be marketed as a hypnotic. The main behavioral effect of the drug in animals was drowsiness and sedation. While many benzodiazepines produce a stimulant effect in the cat, quazepam showed a depressant effect in this species. Studies of the dependence potential of quazepam produced results which suggested a similar profile to that of marketed benzodiazepines. Like diazepam and flurazepam, quazepam potentiated the ethanol-induced loss of righting reflex in mice. One study showed evidence that the hypnotic effect of quazepam may be potentiated by propranolol or alpha-methyldopa. Quazepam produced no significant changes in blood pressure, heart rate, or EKG in the unanesthetized dog when doses (60 mg/kg) large enough to cause ataxia and sedation were used. The four identified metabolites of quazepam produce in the mouse effects which are similar to those of the parent compound both quantitatively and qualitatively, namely, decreased motor activity, increased passivity, decreased muscle tone, decreased visual placing reflex, ataxia, and impairment of righting reflex. The rat was insensitive to quazepam due to rapid metabolism and excretion of the compound in that species. (see below).

SELECTION OF ANIMAL SPECIES FOR LONG TERM TOXICOLOGY STUDIES WITH QUAZEPAM

Pharmacological screening test showed quazepam to be largely inactive in the rat and toxicity studies using doses up to 5000 mg/kg, p.o., or a single dose to Charles River CD rats produced no evidence of toxicity (report P-4287, Schering). A further study showed that daily oral doses of 200 mg/kg for 21 days in the rat elicited no observable effects. To test whether the effect was strain-related, another study (#5003) was performed using eight strains of rat each receiving 1000 mg/kg of drug. Some ataxia and sedation was observed, but the effect was not markedly different among the strains. The observation that quazepam was virtually inactive pharmacologically in the rat came during a study of sedative-hypnotic activity of the drug in a series of accepted tests using either mouse or rat. The series of tests included (study P-4159) hexibarbital potentiation in mice, antagonism of metrazol-induced seizures in mice, taming action in fighting mice, isolation-induced aggression in mice, blockade of mouse-killing (muricide) behavior in rats, conflict procedure in rats, and prevention opiate-induced rigidity in rats. The latter three studies using rats demonstrated only minimal activity of quazepam when compared with similar doses of flurazepam and diazepam. These studies as well as the lack of toxicity of quazepam when given orally to the rats in doses greater than 5000 mg/kg led to the conclusion that the rat would not be a suitable model for long term toxicity testing with quazepam.

In a study comparing absorption, tissue distribution, and excretion of labeled quazepam in rat and mouse (P-4307) the sponsor found that in the rat, quazepam is well absorbed by the oral route but is metabolized and excreted so quickly at tissue levels of drug needed to produce pharmacological effects are not achieved. Thus the rat was found unsuitable for long term toxicity study of quazepam. The hamster was selected for long term studies since that species showed pharmacologic and toxicologic responses to quazepam administration. ADME studies in the hamster further showed metabolic treatment of quazepam in that species to be similar to that found in man (study P-4785).

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Absorption, Distribution, Metabolism, Excretion

Drug metabolism, etc. of quazepam was studied in the mouse, rat, hamster, and squirrel monkey after both oral and i.v. administration. The sponsor has provided an accurate summary of the study data, and this summary is included on the following several pages as part of this review.

NDA 18-708

Absorption, Distribution, Metabolism, Excretion

Drug metabolism, etc. of quazepam was studied in the mouse, rat, hamster, and squirrel monkey after both oral and i.v. administration. The sponsor has provided an accurate summary of the study data, and this summary is included on the following several pages as part of this review.

Drug Metabolism

Synopsis

The absorption, tissue distribution, metabolism and excretion (ADME) of ^{14}C- and/or ^{3}H-quazepam were evaluated in the mouse, rat (pilot study), hamster and squirrel monkey after single oral and intravenous administration.

The metabolic / pharmacokinetic data of quazepam are described for the mouse, hamster, squirrel monkey and man (for comparative purposes only) in Table 1. The excretory (Table 2) and metabolic (Table 3) profiles in animals (mouse, hamster, squirrel monkey) and man are given. The postulated major metabolic pathways are presented in Figure 1.

The major conclusions based upon all studies conducted are:

- Quazepam (orally) is well absorbed by all species studied.
- Quazepam is almost totally metabolized and first pass metabolism is extensive in all species (mouse, hamster, squirrel monkey, man) evaluated. Quazepam's metabolic pattern in these species is qualitatively similar. The metabolites: Sch 15725, Sch 17514, Sch 23309, Sch 23324 are pharmacologically active.
- The plasma half-lives of quazepam and its metabolites vary between species: The shortest half-lives occurred in mouse and hamster, and the longest half-lives were in squirrel monkey and man.

- Quazepam and its metabolites are widely distributed throughout the tissues (mouse, hamster). For most tissues the concentrations of radioactivity are similar to those in plasma. All tissue radioactivity decreased with time and no tissue drug accumulation occurred.
- Quazepam penetrates the placental barrier more readily at near-term (day 18 of pregnancy) than at the end of embryonic formation (day 12). At 18 days, the concentration of radioactivity in fetal tissues are lower than corresponding maternal tissues. Radioactivity disappears at the same rate in the fetus and dam. Radioactivity did not accumulate in fetal tissues. The metabolic profile of quazepam in fetal tissues and maternal plasma was qualitatively similar.
- Quazepam and its metabolites (Sch 15725, Sch 17514, Sch 23309, Sch 23324 and other unidentified metabolites) are excreted in urine and feces, mostly within the first 24 hours after drug administration. A major portion of the quazepam dose (oral, intravenous) is excreted into the urine by the hamster, and into the feces by the mouse; while the squirrel monkey excreted almost the total dose into the feces.
- In mice, quazepam is not an inducer of hepatic drug metabolizing enzyme systems; in hamsters quazepam has only weak induction properties.

- In the rat, the radioactive dose is rapidly and completely absorbed, totally metabolized, and subsequently eliminated very rapidly (mostly in the bile). The resulting very low plasma levels may explain the lack of pharmacologic activity observed in this species.
- The metabolism and excretion pattern of quazepam is similar after intravenous and oral administration.

Table 1. Preclinical metabolic/pharmacokinetic studies with single oral doses of ^{14}C-quazepam.

Pharmacokinteic parameters	Mouse	Hamster	Squirrel Monkey	Man[a]
	(5 mg/kg)	(5 mg/kg)	(10 mg/kg)	(0.4 mg/kg)[b]
Plasma				
Radioactivity				
Tmax (hrs)	1.0	0.5	16.0	1.8
Cmax (ng equiv./ml)	722.8	988.0	2161.0	324.6
$t_{\frac{1}{2}}$ (hrs)	17.8	35.3	43.0[c]	75.6
AUC (ng hr/ml)[d]	6261.8	12467.5	73011.0	11402.3
Quazepam (Sch 16134)				
Tmax (hrs)	0.5	0.25	2.0	1.5
Cmax (ng/ml)	10.1	28.0	34.0	148.0
$t_{\frac{1}{2}}$ (hrs)	1.2	2.4	10.0[c]	39.3
AUC (ng hr/ml)[d]	18.2	24.8	300.0	714.6
2-Oxoquazepam (Sch 15725)				
Tmax (hrs)	0.5	0.25	2.0	1.6
Cmax (ng/ml)	13.2	99.6	41.0	45.6
$t_{\frac{1}{2}}$ (hrs)	1.6	1.9	13.0[c]	40.2
AUC (ng hr/ml)[d]	34.5	49.6	470.0	438.3
N-Desalkylflurazepam (Sch 17514)				
Tmax (hrs)	1.0	0.5	16.0	14.0
Cmax (ng/ml)	219.4	83.6	1416.0	40.9
$t_{\frac{1}{2}}$ (hrs)	1.2	0.6	43.0[c]	69.5
AUC (ng hr/ml)[d]	518.2	107.7	46390.0	3323.4

a = Given for comparative purposes only.
b = 25 mg in an alcoholic solution per subject.
c = approximate value.
d = AUC's are for up to 24 hours for mouse and hamster, 168 hours for squirrel monkey and 120 hours for man.

Table 2. Excretory profile of radioactivity after single doses of ^{14}C-quazepam in animals and man.

Specimen	Percent of Dose Excreted						
	Mouse		Hamster		Squirrel Monkey		Man[a]
	(4 days)		(7 days)		(7 days)		(5 days)
	p.o. (5 mg/kg)	i.v. (5 mg/kg)	p.o. (5 mg/kg)	i.v. (1 mg/kg)	p.o. (10 mg/kg)	i.v. (1 mg/kg)	p.o. (0.4 mg/kg)
Urine	36.6	42.9	53.8	57.3	1.0	1.0	31.3
Feces	61.5	56.9	43.0	40.1	84.0	79.4	22.7
Total	98.1	99.8	96.8	97.4	85.0	80.4	54.0

a = Given for comparative purposes only.

Table 3. Comparative metabolic pattern (relative abundance)[a] of ^{14}C-quazepam in the 24-hour urine (mouse, hamster, man) and 24-hour feces (squirrel monkey).

Compounds*	Mouse	Hamster	Squirrel Monkey	Man[b]
Sch 16134 (Quazepam)	Tr	Tr	Tr	Tr
Sch 15725 (2-Oxoquazepam)	Tr	Tr	+	+
Sch 23324 (3-Hydroxy-2-oxoquazepam)**	+	++	++++	++++
Sch 17514 (N-Desalkylflurazepam)	+	+	+	++
Sch 23309 (3-Hydroxy-N-desalkylflurazepam)**	+++	+++	+	++
Non-identified polar material	++++	+++	+	+

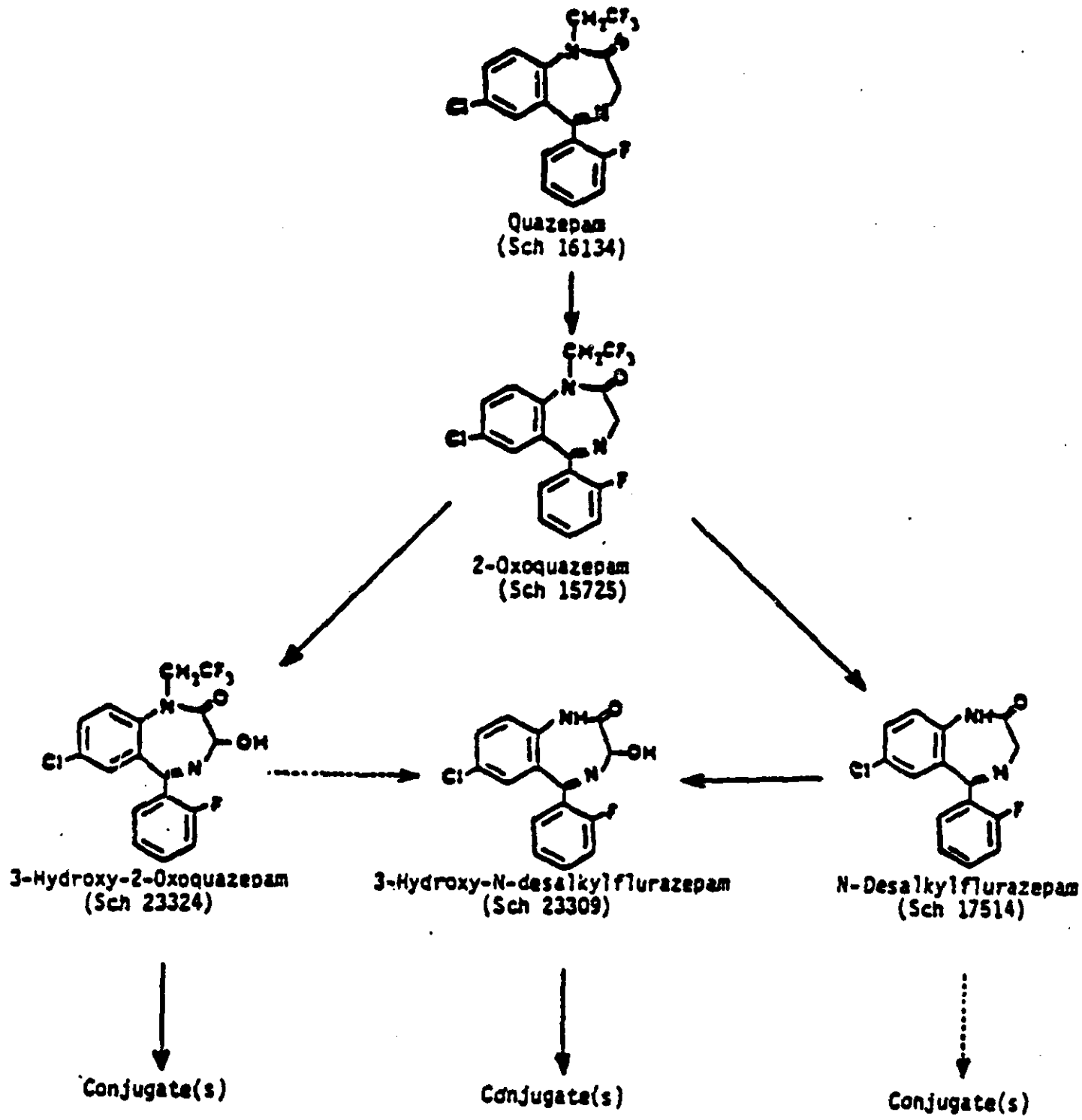
* See structures in Fig. 1.

** Free and conjugated.

a = Tr (trace) ⟶ + (minor) ⟶ ++++ (major)

b = Given for comparative purposes only.

Figure 1. POSTULATED MAJOR METABOLIC PATHWAYS



Preclinical Metabolic Studies: Mouse, Rat, Hamster, Squirrel Monkey

The absorption, tissue distribution, metabolism and excretion of ^{14}C-quazepam were studied in the mouse, hamster and squirrel monkey following single oral and intravenous dosing. These species were selected for metabolic evaluation since they had been used for pharmacologic testing and toxicologic evaluation of quazepam. A pilot study was done in the rat evaluating absorption, tissue distribution and excretion of ^{3}H-quazepam. Additional studies evaluated placental transfer (mouse) and drug induction (mouse, hamster) of quazepam.

In these studies, the concentrations of radioactivity in plasma, urine, feces and other biological specimens were determined by liquid scintillation spectrometry. The concentrations of unchanged quazepam and two metabolites (2-oxoquazepam = Sch 15725; and N-desalkylflurazepam = Sch 17514) in plasma were determined by specific and sensitive gas-liquid chromatographic (GLC) methods. The metabolic profile of quazepam was determined by thin-layer chromatography (TLC). The identified metabolites: Sch 15725, Sch 17514, Sch 23309, Sch 23324 have been shown to be pharmacologically active.

1) Mouse

Method

The absorption, tissue distribution, metabolism and excretion of quazepam were studied in 90 (fifteen groups of 6 animals each) male CD-1 albino mice (20 to 25 grams) following single oral (p.o.) and intravenous (i.v.) dosing with ^{14}C-quazepapm (5 mg/kg).

Absorption

^{14}C-quazepam absorption in mice was rapid and at least 85% complete based upon plasma radioactivity levels (oral) and excretion (oral, intravenous) data.

Mean peak plasma concentrations of radioactivity (723 ng quazepam equiv./ml) occurred 1.0 hour after oral dosing; thereafter, the plasma radioactivity declined with an elimination half-life of approximately 18 hours.

Unchanged ^{14}C-quazepam appeared in plasma very rapidly with peak plasma levels (10 ng/ml) occurring 0.5 hour after drug administration; subsequently plasma ^{14}C-quazepam declined with an elimination half-life of 1.2 hours. At peak plasma concentration, unchanged drug was less than 3% of total plasma radioactivity, indicating that, in the mouse, quazepam underwent extensive first pass metabolism.

Other major components of plasma radioactivity were Sch 15725 (2-oxoquazepam), Sch 17514 (N-desalkylflurazepam, Sch 23324 (3-hydroxy Sch 15725) and conjugated Sch 23309

(3-hydroxy Sch 17514). Sch 15725 reached a peak level (13 ng/ml) 0.5 hour after drug administration and declined with an elimination half-life of 1.6 hours; Sch 17514 reached a maximum level (219 ng/ml) 1.0 hour after dosing and declined with an elimination half-life of 1.2 hours.

Tissue Distribution

Observations at 1, 5 and 24 hours after a single oral dose of ^{14}C-quazepam (5 mg/kg), showed that the highest concentrations of radioactivity were present in the stomach and intestine. For other tissues, the radioactivity relative to plasma concentrated in the liver (1, 5 and 24 hrs) and to a smaller extent in the kidneys (at 1 and 5 hrs), epididymal fat, heart and lungs (at 5 hours). All other tissues which were examined, contained levels of radioactivity equal to or lower than plasma. Most of the radioactivity was cleared from all tissues within 24 hours, indicating that, in the mouse, quazepam and metabolites were not stored in any tissue.

Excretion

After a single oral dose of ^{14}C-quazepam (5 mg/kg), approximately 98% of the dose was excreted (urine, 37%; feces, 61%) within four days; most of the dose (88%) was eliminated during the first 24 hours.

After a single intravenous dose of ^{14}C-quazepam (5 mg/kg), approximately 100% of the dose was excreted (urine, 43%;

feces, 57%) within four days; most of the dose (87%) was excreted during the first 24 hours.

Metabolism

After both oral and intravenous single doses (5 mg/kg) of ^{14}C-quazepam, the mouse excreted the radioactivity in the urine primarily as Sch 23309 (mostly conjugated) and non-identified polar material. Unchanged ^{14}C-quazepam and other quazepam metabolites were present only in small or trace amounts.

Placental Transfer

Method

To evaluate transplacental passage, single oral doses (5 mg/kg) of ^{14}C-quazepam were given to two groups of 12 pregnant mice each, at the post-embryonic period (day 12 of pregnancy) and near-term (day 18 of pregnancy), respectively.

Tissue Distribution

After 12-day pregnant mice received oral ^{14}C-quazepam, the lowest concentrations of radioactivity were present in the amniotic fluid and fetuses. For all time periods (1, 5 and 24 hours post-dose) the mean level of radioactivity in the fetus was 44% of the level measured in maternal plasma. In maternal tissues, the highest concentrations of radioactivity were present in the G-I tract followed by liver, kidneys, ovaries, lungs and brain. The maternal tissue and fetal radioactivity levels

decreased at approximately the same rate as maternal plasma radioactivity during the 5- to 24-hour post-dose period.

In the 18-day pregnant mice who received oral ^{14}C-quazepam, the tissue distribution pattern of radioactivity was similar to the 12-day pregnant mice. At 18 days, fetuses and maternal plasma had similar levels of radioactivity for each time interval (1, 5 and 24 hours post-dose). Furthermore, fetal and maternal tissues had the same distribution pattern of radioactivity; the levels of radioactivity were highest in liver followed by kidneys, lungs and brain. However, fetal tissues contained considerably less radioactivity than the corresponding maternal tissues. Except for amniotic fluid, all tissues (maternal and fetal) contained significantly lower radioactivity at 24 hours than at 5 hours.

Conclusions from these results indicate that:

1. Quazepam and its metabolites crossed the placental barrier more readily on day 18 of pregnancy than on day 12.
2. Concentration of radioactivity in fetal tissues (day 18) were considerably lower than that in corresponding maternal tissues.
3. The radioactivity did not accumulate in the fetal tissues.
4. The radioactivity in the fetuses and maternal plasma had similar metabolic profiles; however, the fetuses had lower amounts of polar metabolites.

2) RAT[14]

Method

In the rat, preliminary studies on absorption, tissue distribution and excretion were evaluated in 73 male Sprague-Dawley rats (250 to 300 grams) with single doses of ^{3}H-quazepam given orally (5 and 10 mg/kg) and intravenously (1 and 5 mg/kg).

Absorption

^{3}H-quazepam was rapidly and totally absorbed after oral administration as indicated by the plasma levels of radioactivity and excretion data. Maximum plasma radioactivity occurred one hour after 10 mg/kg of oral ^{3}H-quazepam, however, the concentrations of radioactivity were low (210 ng quazepam equiv./ml) and decreased rapidly.

Following intravenous dosing (1 mg/kg) the plasma radioactivity declined rapidly from 240 ng quazepam equiv./ml at 5 minutes to 20 ng quazepam equiv./ml at 4 hours.

Tissue Distribution

The concentrations of radioactivity in various tissues after oral (10 mg/kg) and intravenous dosing (1 mg/kg) were generally low except for liver and intestine; lowest concentrations were present in plasma.

Excretion

Biliary excretion of the radioactivity after oral (10 mg/kg) and intravenous (5 mg/kg) ^{3}H-quazepam was rapid and extensive. Approximately 44% of the oral dose and 66% of the intravenous dose, administered to rats with cannulated bile duct, were recovered in the bile within 5 hours.

The rat excreted most of the radioactivity in the feces following either oral or intravenous dosing. Only 10% of the oral and intravenous dose was excreted in the urine over a 4-day period. The radioactivity eliminated in the feces over the same period was 72% of the intravenous dose (5 mg/kg), and 82% to 83% of the oral dose (5 and 10 mg/kg).

The data indicated that after oral and intravenous ^{3}H-quazepam, the rat eliminated drug-related radioactivity rapidly and primarily through the bile. As a result of the rapid elimination, the plasma levels of radioactivity were very low which may explain the lack of pharmacologic activity in the rat.

3) HAMSTER

Method

The absorption, tissue distribution, metabolism and excretion of quazepam were studied in 72 (twelve groups of 6 animals each) male LVC Syrian hamsters (70 to 95 grams) following single oral (5 mg/kg) and intravenous (1 mg/kg) doses of ^{14}C-quazepam.

Absorption

In hamsters, ^{14}C-quazepam absorption was very rapid and at least 94% complete as indicated by the plasma radioactivity and excretion data after oral and intravenous administration. Mean peak plasma concentration of radioactivity (988 ng quazepam equiv./ml) occurred within 0.5 hour of an oral dose of ^{14}C-quazepam; subsequently the plasma radioactivity declined with an elimination half-life of approximately 35 hours.

In plasma, a very small percentage of radioactivity was unchanged drug. At peak level (28 ng/ml), attained 0.25 hours post-dose, unchanged ^{14}C-quazepam accounted for only 3% of plasma radioactivity, indicating that, in the hamster, the drug underwent extensive first pass metabolism. Following peak level, ^{14}C-quazepam declined with an elimination half-life of 2.4 hours.

Other major components of plasma radioactivity were Sch 15725, Sch 17514, Sch 23309 and conjugated Sch 23324. Sch 15725 peaked (100 ng/ml) at 0.25 hours and declined with an elimination half-life of 1.9 hours; Sch 17514 reached maximum level (84 ng/ml) at 0.5 hour and declined with an elimination half-life of 0.6 hours.

Tissue Distribution

After a single oral dose of ^{14}C-quazepam in the hamster, tissue distribution of radioactivity was evaluated at 1, 5 and 24 hours. High concentrations of radioactivity were present in the

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stomach and intestine. For other tissues, the radioactivity relative to plasma concentrated considerably in the liver and to a small extent in the prostate, kidneys, epididymal fat and pituitary. All other tissues investigated contained levels of radioactivity equal to or lower than plasma. For all tissues, the radioactivity was considerably lower at 24 hours than at 1 and 5 hours post-dose. This indicated that ^{14}C-quazepam and its metabolites were not stored in any tissue.

Excretion

Following a single oral dose of ^{14}C-quazepam, approximately 97% of the radioactive dose was excreted (urine, 54%; feces, 43%) over a 7-day period. Similarly, after intravenous administration of ^{14}C-quazepam, approximately 97% of the dose was excreted (urine, 57%; feces, 40%) over a 7-day period.

Metabolism

^{14}C-quazepam was almost totally metabolized in the hamster. Most of the radioactivity excreted in the urine after oral and intravenous dosing was conjugated Sch 23309, conjugated Sch 23324 and non-identified polar material. Unchanged drug and other quazepam metabolites were present only in small or trace amounts.

4) SQUIRREL MONKEY[13]

Method

The absorption, metabolism and excretion of quazepam was investigated in 12 male squirrel monkeys (960 to 1145 grams) following single oral (10 mg/kg) and intravenous (1 mg/kg) doses of ^{14}C-quazepam.

Absorption

In squirrel monkey ^{14}C-quazepam absorption was slow and complete. These conclusions are based upon the plasma levels of radioactivity and excretion patterns after oral and intravenous administration. Mean peak plasma concentration of radioactivity (2161 ng quazepam equiv./ml) occurred 16 hours after oral dosing with ^{14}C-quazepam. Thereafter, the plasma radioactivity declined with an elimination half-life of approximately 43 hours.

Unchanged drug accounted for a very small percentage of total plasma radioactivity. At peak plasma concentration (34 ng/ml), two hours after dosing, unchanged ^{14}C-quazepam represented only 4% of plasma radioactivity, indicating extensive first pass metabolism. Plasma ^{14}C-quazepam declined with an elimination half-life of approximately 10 hours.

Sch 17514 accounted for most of the plasma radioactivity. The plasma concentration of Sch 17514 increased slowly to a peak value of 1416 ng/ml 16 hours after ^{14}C-quazepam oral dosing.

Subsequently Sch 17514 declined with an elimination plasma half-life of approximately 43 hours.

Sch 15725 was also a major component of plasma radioactivity. This compound reached a maximum plasma level (41 ng/ml) two hours after dosing and declined with an elimination half-life of approximately 13 hours.

Following intravenous administration of ^{14}C-quazepam, the plasma radioactivity declined slowly. Unchanged drug, which for the first 15 minutes after dosing represented most of the plasma radioactivity, disappeared from plasma with an elimination half-life of approximately 13 hours.

Excretion

The squirrel monkey excreted the radioactive dose almost totally in the feces. Approximately 79% of the intravenous and 84% of the oral dose were eliminated in the feces over a 7-day period. Only 1% of the dose was excreted in the urine over the 7-day period after either intravenous or oral dosing.

Metabolism

Due to minimal amounts of radioactivity in the urine, the metabolic profile of ^{14}C-quazepam in the squirrel monkey was investigated in the feces following oral and intravenous dosing. Sch 23324 (mostly non-conjugated) was the major metabolite of quazepam in the feces; unchanged drug and other metabolites were present in small amounts.

5) Special Studies:

Liver Drug Metabolizing Enzyme Systems

The effect of quazepam on liver drug metabolizing enzyme systems was evaluated in 24 mice and 4 hamsters after they received high oral doses (100 mg/kg/day) for seven consecutive days. Comparisons were made to a positive control (sodium phenobarbital) and the drug vehicle.

Measurements were made on liver weight, liver to body weight ratio, hepatic microsomal protein, hepatic cytochrome P-450, and the in vitro activities of aniline hydroxylase and benzphetamine N-demethylase.

In mice, quazepam slightly increased liver weight (7%), liver to body weight ratio (9%), and hepatic cytochrome P-450 (47%); quazepam had no effect on the activity of either aniline hydroxylase or benzphetamine N-demethylase.

In hamsters, a considerable increase in hepatic cytochrome P-450 (115%) occurred with quazepam. Although the increase in hepatic microsomal protein was only 22%, and benzphetamine N-demethylation was 32%; aniline hydroxylation was not affected.

QUAZEPAM

ACUTE TOXICITY

Species	Strain	Sex	Age	Route	LD 50
Mouse	CF-1	M		p.o.	5000
Mouse	CF-1	F		p.o.	5000
Mouse	CF-1	M		i.p.	781-928
Mouse	CF-1	F		i.p.	794-1025
Rat	Charles River D	M		p.o.	5000
Rat	Charles River D	F		p.o.	5000
Rat	Charles River D	M		i.p.	3072
Rat	Charles River D	F		i.p.	2749

Observed Effects:

Oral dosage

Mice showed signs of hypoactivity, deep respiration, ptosis, head shaking, ataxia, and straub tail. In the rat, doses of 5000 mg/kg produced no clinical signs.

i.p. dosage

Mice again showed hypoactivity, deep respiration, ptosis, head shaking, ataxia, and straub tail.

Rats given quazepam i.p. showed the following signs near death: prostration, ptosis, slow respiration, oligodipsis, anorexia, hypoactivity, passivity, sluggishness, ataxia, piloerection, and chromodacryorrhea.

Beagle dogs receiving 1000 mg/kg p.o. showed excitement and salivation. During the excitement stage there was a rise in body temperature, heart rate and respiration rate.

Table II. – ACUTE TOXICITY OF BENZODIAZEPINES IN MICE

Route	QUAZEPAM	TEMAZEPAM	OXAZEPAM	CHLORDIAZEPOXIDE	DIAZEPAM	LORAZEPAM	CLODIAZAM
Oral	>5000[a]	800–1900	>5000	794(735-857)	1901(1632-2214)	>5000	600(504-918)[a]
	>5000[b]						820(686-980)[b]
I.P.	845(781-928)[a]	909-1700	>5000	401(341-473)	774(732-819)	873.6	510(442-586)[a]
	921(794-1025)[b]						615(515-708)[b]

LD_{50} mg/kg (fiducial limits p = 0.95)

[a] – male
[b] – female

Table III. - ACUTE TOXICITY OF BENZODIAZEPINES IN RATS

ROUTE	QUAZEPAM	TEMAZEPAM	OXAZEPAM	CHLORDIAZEPOXIDE	DIAZEPAM	LORAZEPAM	CLOBAZAM
Oral	>5000[a]	2000-8000	>5000	537(472-611)	1517(1237-1862)	>5010	6000(4880-7380)
	>5000[b]						
I.P.	3072(2569-3635)[a]	600	>5000	276(247-309)	661(542-805)	005(753-0611)	740-1526
	2749[b]						

LD_{50} mg/kg (fiducial limits p = 0.95)

[a] - male
[b] - female

CHRONIC TOXICITY STUDIES

One-Year Toxicity in Hamster

Animal: LVG Syrian Hamsters

Dose: 0, 3, 20, 120 mg/kg daily in diet

No. and Sex per group: 36M, 36F (72M, 72F in control)

Interim Sacrifice: none, except for moribund

Duration: 51 weeks

The doses used in this study ranged from 5 to 200 times the maximum proposed human dose of 0.6 mg/kg. For comparison, one group of hamsters was treated with diazepam at 120 mg/kg/day.

Observed Effects:

The sponsor used the hamster for long-term toxicity because the drug is rapidly metabolized in the rat and the toxicity profile of quazepam in hamsters is similar to that of 1,4 benzodiazepines in other rodent species. Dose-related ataxia was observed in males and females given quazepam as well as in the hamsters given diazepam. Incidence and degree of ataxia was similar at 120 mg/kg for both diazepam and quazepam treated hamsters. Both drugs caused alopecia after three to six months. Tremors, teeth chattering, and increased activity were noted at all doses of quazepam and in diazepam-treated hamsters. There was no other condition observed that was thought to be drug related.

Doses selected for the study were based on the results of a 30-day pilot toxicity study where it was found that liver weights were increased at the 125 mg/kg level and transaminase values were increased at the 250 mg/kg level.

animals dying or killed in moribund condition

Mortality

Quazepam dose (mg/kg)	0	3	20	120	120 diazepam
males	23/72	19/36	9/36	14/26	9/36
females	53/72	21/36	21/36	25/36	16/36

Microscopic examination showed that the hamsters in all groups generally died from enteritis, atrial strombosis and heart failure, or renal amyloidosis and uremia. These diseases were considered sponsaneous and unrelated to dosing.

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Body weight/food consumption/water consumption

Body weight gains were higher than controls in HD and diazepam groups, amounting to an increase of 5-9 grams in group mean body weights for those groups. Only males were affected. During the post-dose washout period, lost body weight was recovered. Males in all dosage groups showed slightly higher food consumption than controls.

Hematology and blood chemistry

No compound-related changes were observed in the hematology values. The group mean cholesterol values were statistically significantly less than controls in the MD group, HD group and diazepam group (females only) at weeks 13 and 25. Group mean albumin/globulin ratios in HD and diazepam treated hamsters were slightly greater than control values. The significance of these findings is unclear at this point.

Urinalysis

The 24-hour urine volumes of treated females tended to be higher than control values. There was a corresponding increase in water intake by these hamsters, which also tended to produce urine with below normal osmolality or specific gravity. The changes were not related to dose and are considered to be of little biological significance since the changes were small and disappeared over time.

Ophthalmic examination:

Eyes of all hamsters were examined once during the acclimation period. All hamsters (except those bled for clinical pathology measurements or compound plasma determination) were also examined during weeks 24 and 51 of the closing period and at post dose week 5. In each case, eyes were examined with a Fison indirect ophthalmoscope. No ocular changes were found in any of the hamsters, except for physical injury caused by an orbital sinus bleeding procedure.

Organ Weights

Group	Organ showing small mean relative weight change
high dose males	+liver, +kidney, +adrenal
high dose females	-kidney, -adrenal
mid dose females	-adrenals, -ovaries
diazepam males	+liver, -seminal vesicles
diazepam females	-adrenal, -kidney

Obviously, no conclusion can be drawn from the sporadic occurrences.

Gross Pathology

No compound-treated changes were seen at necropsy in any of the hamsters in this study. Alopecia was observed in all groups with a slightly higher incidence in the treated groups. Gross lesions observed were either spontaneous or caused during sacrifice.

Histopathology

In HD hamsters, bile retention in the liver occurred in 22/27 males and and 7/30 females necropsied during the study or at the scheduled necropsy. Benzodiazepine-induced bile stasis has been reported in other species. Hepatocellular hypertrophy in treated hamsters was seen in 4/25 HD males, 2/27 HD males, and 2/36 HD females. In hamsters which were sacrificed during the postdose observation period, hepatocellular hypertrophy occurred in 2/11 MD males and 1/9 HD males. Bile retention was observed in the liver of 1/24 diazepam males during study and 4/12 diazepam males sacrificed in the post dose period. Hepatocellular hypertrophy occurred at 1/24 in the males getting diazepam (during study) and at a frequency of 1/12 in the group killed after the post dose period. Many hamsters showed signs of salmonellosis and phlebothrombosis and this was considered to be incidental to treatment. Other spontaneous diseases included enteritis, atrial thrombosis and heart failure, and renal amyloidosis and uremia.

Since most observed toxic effects of quazepam occurred at the 120 mg/kg dose level (200 x the maximum proposed human dose) it would be safe to assume that a maximally tolerated dose for quazepam would lie at somewhat less than 120 mg/kg, but greater than 20 mg/kg daily.

HAMSTER CHRONIC TOXICITY

Summary and Evaluation

The number of animals used, duration of the study, and dosage range employed were acceptable for this type of long term toxicity in the rodent. The dose range employed was sufficient both to demonstrate evidence of toxicity as well as allow for acceptable long term survival of the animals. Diazepam was given as a comparative control in a dose sufficient to cause toxic signs. Mortality among the hamsters was equally divided between dosed and control groups, and was attributed to enteritis, atrial thrombosis, and heart failure, or renal amyloidosis and uremia. These conditions were regarded as spontaneous and not drug related. Both diazepam and quazepam elicited ataxia, alopecia, tremors, and hyperactivity at the 120 mg/kg level. While neither drug altered water consumption, both drugs were associated with enhanced body weight and food consumption in the males at the 120 mg/kg dose. Only those females receiving diazepam experienced an increase in food consumption. The drugs did not alter hematology or clinical chemistry values, and drug related gross physical changes were not seen at necropsy. Histopathology revealed only bile retention as a significant finding and only at the high dose level (120 mg/kg). Bile stasis is known to be produced by other benzodiazepines in other species as well.

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One Year Monkey Toxicity

Animal: squirrel monkey (Solmiri sciureus)

Dose: 0, 2, 10, 50 mg/kg P.O. by gavage

No. and Sex per Group: 5M, 5F

Duration: 52 weeks (no interim sacrifice)

Doses used were up to 83 times the proposed maximum human dose of 0.6 mg/kg/day. One group of monkeys, for comparison, was treated with 50 mg/kg diazepam (about 63 times the 40 mg/day therapeutic dose for man). Two monkeys from each group were observed during a 4-week post dose period.

Mortality

1 control female, 1 LD male. Deteriorating health preceded death. During the 4 week post-dose period 1 LD male, 1 MD male, and all 4 diazepam treated monkeys died or were sacrificed in poor condition. Their body weights had decreased considerably and the animals had shown repeated bouts of convulsions. Pale livers, kidneys, and fatty degeneration of the liver were noted.

Gross Observations

Dose and drug-related sedation, somnolence, ataxia, and tremors were observed in monkeys taking either drug. Frequency and degree was greatest during first three weeks of study. During the first week of study, several HD and diazepam treated monkeys were unable to move without falling. There were also incidental findings of alopecia, lacrimation, emesis, foot and tail sores and ulcers, tooth absesses, salivation, and distended abdomen.

Ophthalmoscopic Examination

These tests using a Fison indirect ophthalmoscope, before the start of the study and again at weeks 24 and 48 of the dosing period and at post dose week 4 did not reveal any ocular changes attributable to dosing with either quazepam or diazepam.

Evidence of Possible Addiction Liability

During the 4 week post dose period, the clinical signs were similar for the monkeys in the diazepam and quazepam groups; ataxia, emesis, tremors, or convulsions were observed within 3 days after cessation of dosing. The convulsions usually lasted for only a few minutes and were followed by either complete recovery or death. One monkey found convulsing, prostrate, and near death on the eigth day of the post dose period was redosed with a single dose of diazepam. This monkey showed signs of recovery in 20 minutes and appeared relatively healthy for about 3 days when it again convulsed. The monkey was found dead about 9 days after being redosed with diazepam.

Body Weight and Food Consumption

Group mean values for body weight and food consumption did not differ appeciably among the groups.

Other Effects

On day 1, a dose-related decrease occurred in mean values for body temperature, heart rate, and respiration rate. Thereafter, mean values for these parameters did not differ significantly from control values. Few drug related changes were revealed in the clinical laboratory determinations. High alkaline phosphatase levels (330 IU/L) were found in HD females only. Compound-related increases in SGPT values were observed in 3 HD males and 4 HD females. The values were elevated (851U/L) in males at weeks 2, 13, 26, 452, and in females at weeks 13 and 52. Slight elevations in SGOT values were observed also in 2 females at week 13 and in 3 males at weeks 2 and 13. No compound-related changes were seen in urine chemistry values.

Evidence of Possible Addiction Liability

During the 4 week post dose period, the clinical signs were similar for the monkeys in the diazepam and quazepam groups; ataxia, emesis, tremors, or convulsions were observed within 3 days after cessation of dosing. The convulsions usually lasted for only a few minutes and were followed by either complete recovery or death. One monkey found convulsing, prostrate, and near death on the eigth day of the post dose period was redosed with a single dose of diazepam. This monkey showed signs of recovery in 20 minutes and appeared relatively healthy for about 3 days when it again convulsed. The monkey was found dead about 9 days after being redosed with diazepam.

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Gross Pathology

Organ Weights		Individual Organ Weights (mg)		
Dose mg/kg	# animals	Tests	Prostate	Seminal Vesicles
0	3	3.78	0.73	1.71
		3.05	0.32	0.89
		4.22	0.77	2.57
diazepam 50	3	3.73	0.35	0.68
		0.62	0.04	0.12
		1.58	0.18	0.33
2	2	2.72	0.42	1.15
		3.40	0.78	1.80
10	3	3.99	0.75	1.56
		2.23	0.48	0.80
		2.01	0.39	0.93
50	3	3.08	0.27	0.56
		2.44	0.35	0.85
		2.92	0.14	0.69

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Ratios Organ Weight/Body Weight (Males)

Dose mg/kg	# of Animals	Testes	Prostate	Seminal Vesicles	Liver
0	3	0.357	0.069	0.161	1.509
		0.355	0.037	0.103	1.686
		0.391	0.971	0.238	1.602
diazepam 50	3	0.397	0.037	0.072	2.181
		0.089	0.006	0.017	2.343
		0.247	0.028	0.052	2.703
2	2	0.247	0.038	0.105	1.645
		0.340	0.078	0.180	1.450
10	3	0.403	0.076	0.158	1.687
		0.259	0.056	0.093	1.779
		0.251	0.049	0.116	1.700
50	3	0.376	0.033	0.068	2.037
		0.284	0.041	0.099	1.930
		0.332	0.016	0.078	2.034

Ratios Organ Weight/Body Weight (Females)

Dose mg/kg	# Animals	Liver
0	2	2.049
		2.316
diazepam 50	3	3.000
		2.896
		2.808
2	3	1.855
		1.712
		1.869
10	3	2.238
		2.403
		2.517
50	3	2.055
		2.167
		1.809

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At the end of the 52 week study, the absolute and relative weights of the testes and prostate and seminal vesicles were below control valvues in HD males. In the diazepam group the same holds true (see tables above). The relative weights of the testes were below control values in 2 LD and 2 MD monkeys. The absolute weights of the testes were below the control values in LD and MD monkeys. The relative liver weights were higher than control values for both males and females at the HD quazepam level and in the diazepam group.

Except for decreased size of the genitals in one diazepam treated male, no compound related lesions were reported on gross examination.

Microscopic examination showed small foci of necrosis in the livers of 2 HD females and 1 HD male. Fatty change in the liver was moderate in 1 MD and 1 HD male and severe in 1 LD female. The fatty change was attributed to mobilization of body fat and its deposition in the liver secondary to poor health of the monkeys. The decreased testicular weights observed in some monkeys could not be accounted for by microscopic findings except for atrophic gonadal adnexa observed in 2 MD males. Diazepam treated monkeys showed atrophy of gonadal adnexa in 2 of the 3 monkeys examined.

Incidental findings included lung lesions (interstitial pneumonia, atalectasis and lymphomonocytic infiltrates) and intestinal inflammation secondary to parasitic infection. One LD female had an adrenal adenoma and a thyroid adenoma.

MONKEY CHRONIC TOXICITY

Summary and Evaluation

Squirrel monkeys were chosen for the test to fulfill the requirement for a nonrodent test model after preliminary experiments showed quazepam to be pharmacologically active in this species. The dose of drug selected for the test were based on the results of a pilot 13 week study. In that study a dose of 50 mg/kg was well tolerated, but during a post dose recovery period, signs of withdrawal occurred including hyperactivity convulsions, and decreased food consumption. For the one year study, doses of 2, 10, and 50 mg/kg were employed as was a 50 mg/kg diazepam treated group. The quazepam doses were 3, 17 and 83 times for proposed human dose of 0.6 mg/kg maximum. The number of animals employed was adequate at 5 M and 5 F per dose group. Three monkeys of each sex groups were killed and examined at the end of 52 weeks. The remaining 2 of each groups were killed after a 4 week post-test washout period. All monkeys survived the 52 week test period except for 1 control and one quazepam treated low dose monkey. Of the monkeys retained for the 4 week post dose followup, several in both diazepam and quazepam groups died or were killed in moribund condition. Weight loss and convulsions were observed in these animals, probably a reaction to withdrawal of the drug. The principal behavior changes during the test were sedation, somnolence, ataxia, and tremor. These occurred with both diazepam and quazepam. Hematology, blood chemistry, and urine chemistry determination revealed no meaningful compound related effects. Sporadic adverse findings at necropsy did not appear drug relateo and were generally attributed to the poor condition of several monkeys at the end of the testing period.

Reproduction and Teratology Studies

NDA 18-708

Fertility and General Reproductive Performance of the Mouse - Segment I

Animal: Charles River CD-1 mouse

Dosage: 0, 6, 18, 54 mg/kg daily by intubation; positive control with 54 mg/kg diazepam

per group: 15 males, 30 females

Treatment

Males at least 6 weeks old were treated for 8 weeks prior to mating to test for effects of drug on spermatogenesis. Females, sexually mature, were treated for 2 weeks prior to mating the through mating, gestation, and lactation. Dosing continued until sacrifice of the F0 generation after selection of F1 animals. In each group, 14 females were killed on day 17 of gestation to see effects of drug on *in utero* development, while 15 or 16 females in each group were allowed to rear litters to 21 days postpartum to assess drug effect on parturition, lactation, and post-natal development and behavior of offspring.

Observed Effects and Mortalities

In all test groups treatment with quazepam was associated with dose-related sedation. Degree of sedation was similar in HD and diazepam groups. One control female died and one male and female from each of HD and diazepam groups were killed due to deterioration of condition. Body weights and food consumption were relatively unaffected.

	Dose mg/kg				
Mating performance: Males	0	6	18	54	diazepam 54
# Males successfully impregnating 2 females:	15/15	15/15	10/15	8/15	10/15
Impregnating 1 of 2 females	0/15	0/15	4/15	5/15	5/15

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Mating performance: Females	Dose mg/kg 0	6	18	54	diazepam 54
# Females paired	30	30	30	30	29
# did not mate	2	3	5	5	5
pregnancy rate %	100	100	80	70	83
Data from 16 dams allowed to litter:					
# live young	11.9	11.3	9.6	10.8	11.4
# embryonic deaths	0.9	1.2	1.4	2.3	1.2
Implantations	12.7	12.7	11.0	13.0	12.6
% post-implantation loss	6.7	10.1	13.0	17.0	9.9
% pup loss by day 21 pp	11	24	28	79	80

A reduced number of pregnancies was found at MD, HD, and diazepam. The lower pregnancy rate was associated with reduced numbers of dams showing clear evidence of mating. Duration of gestation was essentially comparable for all groups. The table above shows a correlation between increasing dose and decreased pregnancy rate, increased embryonic death, increased post-implantation loss and increased total pup loss. There was no evidence of unusual fetal abnormalities. It is apparent that quazepam interferes with reproductive performance in the mouse when given at doses of over 60x the proposed human dose.

F1 generation:

It was hard to assess the effect of quazepam on the generation because of the severe loss of pups in the MD and HD groups. Data available for LD and MD groups show some retarded development at MD, little or no effect at LD.

Results from most of the tests in this study suggest that the 54 mg/kg dose of quazepam produces qualitative and quantitative results similar to those seen with 54 mg/kg diazepam.

Teratology Studies in Mouse and Rabbit

A. MOUSE TERATOLOGY

per group: 25

Species: Charles River CD-1 strain mice

Dose: 0, 3, 20, 120 mg/kg/day from day 6-15 after mating, killed on day 18

Positive control: diazepam 160 mg/kg/day

Doses of quazepam used were about 5, 33, and 200x the clinical dosage. Diazepam was used also at about 200x the clinical dosage. The study is to determine the effects of the drug on fetal development. Drug was given by esophageal intubation.

Maternal Findings

All mice in HD group are hypoactive from within a half hour up to 3 hours after being dosed. Same for diazepam group. Two mice died from aspirating the drug suspension. Dams that survived to the end of the study showed no unusual clinical signs at time of sacrifice. The percentage of mice in each treated group and diazepam group that became pregnant was not significantly different from that in control (see table). There was also no real difference between treated and control in mean number of implantations, resorptions, and the percentage of dams/group that had resorptions. HD and diazepam treated dams ate more and gained weight by the end of the study (day 15) but lost the weight during the 3 day post-dosing period.

Offspring

Litter size, fetal distribution in utero, sex distribution, and fetal body weights were comparable between treated and controls.

Seven of the 1036 pups examined had major malformations, one in a quazepam-treated mouse and 6 in diazepam treated mice. There was some minor skeletal variations observed such as extra ribs and fused ribs. Retarded ossificaton of sternabrae, vertebrae, distal phalanges and suproccipital bones was greater in the fetuses of MD, HD and diazepam mice when compared with control, but still within the "normal" range according to literature reports. This is a common mouse variant and has been

reported to range in incidence fro 2-93% in this strain of mouse. The sponsor speculates that reduced food consumption in the dams in these treatment groups may be a contributing factor in the incidence of retarded ossification observed.

Essentially quazepam does not appear to be a teratogen in the mouse although high doses (200x human dose) of quazepam as well as diazepam may slow the process of bone ossification.

STUDY No. 78009
SCH 16134 IN MICE - SCHEDULE II

Mouse Segment II

TABLE 2. Summary of Reproduction Data

		SCH 16134				
	Control	3.0mg/kg[a]	20mg/kg	120mg/kg[a]	Positive Control[1,a]	P-value
Total Mated	25	25	25	25	25	
No. Pregnant	19	17	19	21	22	
% Pregnant	76	68	76	84	88	p>.10
No. Remaining Preg. to Day 18	18	17	19	21	21	
No. That Died Before Day 18	0	0	0	1	1	
Total No. of Implantations	226	183	210	234	247	
Mean ± S.E.	11.8 ± 0.3	11.4 ± 0.4	11.6 ± 0.3	11.7 ± 0.6	11.8 ± 0.8	p>.10
Total No. of Resorptions	14	16	27	19	18	
Mean ± S.E.	0.7 ± 0.3	1.0 ± 0.3	1.4 ± 0.3	1.0 ± 0.2	0.9 ± 0.2	p>.10
No. of Females Resorbing	8	10	13	12	13	
%	42	63	68	60	62	p>.10
No. of Litters	19	16	19	20	21	
No. of Live Offspring	208	166	190	215	229	
No. of Dead Offspring	3	1	1	0	0	
Mean Litter Size No. ± S.E.	11.1 ± 0.3	10.5 ± 0.3	10.1 ± 0.5	10.8 ± 0.4	10.9 ± 0.5	p>.10

[a] Per Max Klein, mouse #42 in the 3 mg/kg group and mouse #88 in the 120 mg/kg group delivered prior to sacrifice on Day 18 and are excluded from the statistical analyses on implantations, number of litters, litter size, sex distribution, and body weights of offspring. Mouse #123 in the positive control group died and resorbed all conceptuses and is included only in pregnancy rate analysis.

[1] SCH 9584 (Diazepam, 160 mg/kg).

STUDY NO. 79009
SCH 16134 IN MICE - SEGMENT II

Mouse Segment II

TABLE 2 (cont.). Summary of Reproduction Data

	Control	SCH 16134 3.0mg/kg	SCH 16134 20mg/kg	SCH 16134 120mg/kg	Positive Control[1]	P-value
Distribution of Offspring in Uterus						
No. in Left Horn	102	75	96	103	117	
No. in Right Horn	109	92	95	112	112	
% in Left Horn	48	45	50	48	51	p>.10
Distribution of Males and Females						
No. of Males	114	88	98	114	120	
No. of Females	97	79	93	101	109	
% Males	54	53	51	53	52	p>.10

[1] SCH 9584 (Diazepam), 160 mg/kg.

TABLE 3. Findings of Soft Tissue and Skeletal Examination

	Vehicle Control	SCH 16134 3.0 mg/kg	SCH 16134 20.0 mg/kg	SCH 16134 120.0 mg/kg	Positive Control (Diazepam) 160.0 mg/kg
Number Delivered	208 (212)	166 (178)	190 (191)	215 (225)	229 (230)
No. Examined For:					
a) Soft Tissue Defects	62 (64)	51 (55)	60 (61)	70 (73)	75
b) Skeletal Defects	146 (148)	115 (123)	130	145 (152)	154 (155)
Major Malformations					
No. With Cleft Palate	0	1	0	0	3
No. With Exencephaly	0	0	0	0	1*
No. With Open Eyelids	0	0	0	0	2 (3)
Total No. With Major Malformations	0	1	0	0	5 (6)
Minor Developmental Variations					
No. With Dilated Renal Pelves	0	0	0	1	2
Extra Cervical Ribs					
a) Single	2 (2)	5 (9)	8	7	7
b) Pair	5 (5)	2 (3)	5	8	1
Extra Thoracic Ribs					
a) Single	18 (18)	5	16	24	16
b) Pair	30 (31)	18 (19)	23	32	21
Unossified Distal Phalanges	0	1	1	2 (6)	9 (10)

Note: Those values in parentheses also include the findings from late resorptions, dead pups, and offspring delivered early.

* This pup also had open eyelids.

TABLE 3 (cont.). Findings of Soft Tissue and Skeletal Examination

	Vehicle Control	SCH 16134 3.0 mg/kg	SCH 16134 20.0 mg/kg	SCH 16134 120.0 mg/kg	Positive Control (Diazepam) 160.0 mg/kg
Sternebrae					
a) Unossified	0	0	2	1 (2)	8
b) Bipartite	4 (5)	2	9	11 (12)	5
c) Reduced Ossification	0	0	1	0 (0)	4
d) Assym-metrical	0	2	1	0 (0)	1
Unossified Caudal Vertebrae	0	0	0	1 (2)	0 (1)
Reduced Ossif. of Ischium and Pubis	0	0	0	1	0
Cervical Vertebrae					
a) Unossified	0	0	0	0 (1)	0
b) Unossified Centra	0	0	0	1 (3)	2
c) Hemicentra	1	0	0	0	0
Supraoccipitals					
a) Bipartite	0	0	6	3 (4)	8
b) Reduced Ossification	1	0	1	1	0 (1)
c) Assym-metrical	1	0	0	0	1
Fused Ribs	1	1	0	0	0
Total # With Minor Variations	63 (64)	37 (42)	73	92 (103)	83 (86)
% With Minor Variations	30	22 (24)	38	43 (46)	36 (37)

Note: The incidences of retarded ossification (based on no. examined for skeletal defects) in the vehicle control, 3 mg/kg, 20 mg/kg, 120 mg/kg and in the positive control groups were 5%, 5%, 16%, 15% and 25%, respectively.

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B. RABBIT TERATOLOGY

Species: New Zealand White Rabbits (average weight = 3.8 kg)

per group: 14 treated, 16 control

Dose: 0, 10, 20, 40 mg/kg daily by intubation from day 6-18 after mating, killed on day 30 after mating. No diazepam control was used.

Maternal Findings

Some animals from each treatment group as well as controls developed sicknesses that included anorexia, congested lungs, pyrometra, snuffles, ruptured stomach -- none of which occurrences could be correlated with drug administration.

Incidence: 4 control, 4 LD, 3 MD, 5 HD

Other Findings (maternal):	0	LD	MD	HD
Pregnancy rate (%)	81	86	93	85
Implantation	101	113	113	111
Resorptions	20	15	11	21

Offspring	0	LD	MD	HD
Litter size	81	96	92	81
Mean litter size	7.4	9.6	7.7	8.1
Percent males	52	55	46	46
Body Weight	52	46	47	41
24 hr. survival (%)	94	100	100	96

The above tables show a lack of variation in the measured parameters between control and treated rabbits and offspring.

The incidence of minor variations in development in each of the treatment groups was not significantly different from that in controls. The variations consisted of extra ribs and to a lesser extent of retarded ossification of the sternabrae. Only 2 of the 350 pups produced in the study were "abnormal." One MD pup was missing a tail and one HD pup had an umbilical hernia. The data in this study support the sponsor's view that quazepam is not teratogenic in the rabbit.

NDA 18-708

Segment III Reproduction Study in Mice
(Peri and Post natal)
First of 2 identical studies

Animal: albino mice (Charles River CD-1)

per group: 25F

Dosage group: 0, 3, 9, 18 mg/kg from day 13 after mating to day 21 post-partum diazepam 18 mg/kg was positive control

The mice were allowed to deliver naturally and to rear their offspring to day 21 after parturition at which time dame and offspring were sacrificed. Dose of quazepam were 5, 15, and 30x the proposed maximum human clinical dose of 0.6 mg/kg daily. Diazepam dose used was about 23x its clinical dose of 0.8 mg/kg.

Transient hypoactivity occurred in MD and HD as well as diazepam control mice. Eight mice died, mostly because of lung congestion. Twenty-four mice were killed before end of study because their litters had died. Two of those were control and the others were almost equally distributed among the treated groups.

Length of gestation, labor, litter size, and sex distribution of offspring were not affected by either drug. Mean body weights of offspring in MD, HD and diazepam groups were less than that of vehicle controls on day 4 after birth but by day 21 their body weightrs were comparable to vehicle controls.

Offspring deaths during lactation were increased in all treated groups, mostly occurring between birth and day 4 after birth and attributed to maternal neglect due to drug effect.

Renal changes in the form of hydronephrosis and dilated renal pelves were seen in the offspring of all groups.

Renal Changes

Dose mg/kg	Incidence %
0	0.8
3	2.9
9	4.8
18	9.2
diazepam 18	2.8

This study was repeated to determine if the above renal findings were accepted. The following tables contain a summary of the reproduction data in this study.

Table 2. Summary of Reproduction Data

	SCH 16134					
	Control	3 mg/kg	9 mg/kg	18 mg/kg	Diazepam (18 mg/kg)	Overall P-values (NS = p>.10)
Gestation Length (from Day 0)						
Mean (Days) ± S.E.M.	19.0 ± 0.05 (N=21)	19.1 ± 0.10 (N=22)	19.1 ± 0.06 (N=22)	19.2 ± 0.13 (N=23)	19.0 ± 0.00 (N=22)	NS
Total No. of Implantations	268	280	285	[illegible]	281	
Mean ± S.E.M.	[illegible] (N=21)	[illegible] (N=22)	[illegible] (N=22)	[illegible] (N=23)	12.8 ± 0.40 (N=22)	NS
Total No. Born	254	245	252	261	246	
Mean/Litter ± S.E.M.	12.1 ± 0.31 (N=21)	11.1 ± 0.51 (N=22)	11.5 ± 0.47 (N=22)	11.4 ± 0.45 (N=23)	11.2 ± 0.38 (N=22)	NS
Offspring Deaths[1]						
Day 0 (Birth)						
No. Born	229	198	240	251	246	
No. Dead	4	4	9	12	12	
% Dead	1.7%	2.0%	3.8%	4.8%	4.9%	NS
Days 1-4						
No. Born Alive	225	194	231	239	234	
No. Dead	3	31	62	60	56	
% Dead	1.3%	** 16.0%	*** 26.8%	*** 25.1%	*** 23.9%	p<.01
Days 5-21						
No. Alive Day 4	222	163	169	179	178	
No. Dead	39	27	42	44	27	
% Dead	17.6%	16.6%	24.9%	24.6%	15.2%	NS
Days 0-21						
No. Born	229	198	240	251	246	
No. Dead	46	62	113	116	95	
% Dead	20.1%	** 31.3%	*** 47.1%	*** 46.2%	*** 38.6%	p<.01

** Significantly different from control, p<.05.

*** Significantly different from control, p<.01.

1 [illegible] offspring [illegible] the post-operative period were not to be included in these analyses since the deaths

Table 2. Summary - Reproduction Data (cont'd)

	ACH 161 36					
	Control	1 mg/kg	2 mg/kg	10 mg/kg	Pterygon (10 mg/kg)	Overall F-values (NS = p>.10)
Sex Distribution						
Day 0						
No. Males	125	106	130	136	115	
No. Females	102	92	109	114	131	
% Males	55%	53%	54%	54%	47%	NS
Day 21						
No. Males	102	76	71	79	73	
No. Females	81	60	56	56	78	
% Males	56%	56%	56%	58%	48%	NS

NDA 18-708

Repeat of Mouse Segment III Study
(Second of 2 studies)

Animal: Mouse (Charles River CD-1)

per group: 25F

Dosage groups: 0, 9, 18 mg/kg p.o. from day 13 after mating to day 21 post partum diazepam 18 mg/kg was positive control.

Doses used were 15 and 30x proposed human doses. Diazepam control dose was 23x human dose.

Transient hypoactivity occurred in all treated mice. Length of gestation, labor, litter size, sex distribution of offspring and incidence of offspring mortality were not affected by either of the drugs. Mean body weights of offspring in the HD and diazepam groups were reduced compared to control. Of the 284 pups sacrificed on day of birth only one had a defect (dilated renal pelvis) and was from the vehicle control group. None of the pups examined which survived to day 21 or any of those that died during lactation showed hydronephrosis or dilated renal pelves. These findings are in contrast to the previous segment III mouse study using the same techniques and protocol. It is also surprising that the incidence of pup death that was observed previously and attributed to ~~maternal~~ neglect due to drug effect was not seen in the present study.
maternal

TABLE 21: Summary of Reproduction Data

	GCH 16134				
	Control	2 mg/kg	10 mg/kg	Pierson (10 mg/kg)	Overall P-value (NS = p>.10)
Gestation Length (from Day 0)					
Mean (Days) ± S.E.M.	18.9 ± 0.09 (n = 25)	19.0 ± 0.14 (n = 19)	18.8 ± 0.09 (n = 21)	18.7 ± 0.10 (n = 22)	NS
Total No. of Implantations					
Mean ± S.E.M.	12.0 ± 0.38 (n = 25)	12.0 ± 0.41 (n = 19)	12.3 ± 0.34 (n = 21)	12.5 ± 0.33 (n = 22)	NS
Total No. Born					
Mean/Litter ± S.E.M.	10.7 ± 0.48 (n = 25)	11.0 ± 0.49 (n = 19)	11.1 ± 0.37 (n = 21)	11.1 ± 0.49 (n = 22)	NS
Offspring Deaths[1]					
Day 0 (Birth)					
No. Born	188	148	163	171	
No. Dead	7	8	2	1	
% Dead	3.7%	5.4%	1.2%	0.6%	p>.10 for all comparisons
Days 1-4					
No. Born Alive	181	140	161	170	
No. Dead	10	6	17	19	
% Dead	5.5%	4.3%	10.6%	11.2%	p>.10 for all comparisons
Days 5-21					
No. Alive Day 4	171	134	144	151	
No. Dead	28	12	12	24	
% Dead	16.4%	9.0%	8.3%	15.9%	p>.10 for all comparisons
Days 0-21					
No. Born	188	148	163	171	
No. Dead	45	26	31	44	
% Dead	23.9%	17.6%	19.0%	25.7%	p>.10 for all comparisons

[1] About one-third of the offspring from each litter was sacrificed on the day of birth for soft tissue examination; these offspring were excluded from these analyses.

TABLE 2: Summary of Reproduction Data (Continued)

	BCH 1613A				
	Control	2 mg/kg	10 mg/kg	Pisarro (10 mg/kg)	Overall P-values (NS = p>.10)
Sex Distribution					
Day 0					
No. Males	123	99	120	122	
No. Females	140	110	112	123	
% Males	47%	47%	52%	50%	NS
Day 21[1]					
No. Males	65	51	66	58	
No. Females	78	65	66	69	
% Males	45%	47%	50%	46%	NS

[1] It should be noted that about one-third of the offspring from each litter were sacrificed on day 0; therefore the day 0 analysis includes these offspring but the day 21 analysis excludes them.

CARCINOGENICITY STUDIES

Statistical Analysis of Data From Carcinogenicity Studies

Incidence of lesions were analyzed using Fisher's Exact Test. Test data were subjected to a statistical evaluation of variance with the F-MAX test. When differences between groups variances were not significant ($P > 0.01$) a one-way analysis of variance (ANOVA) was performed. If significant differences ($P \simeq 0.10$) among the means were indicated by the ANOVA, Dunnett's test was used to determine which means were different from the controls. When the difference between group variances were significant ($P \leq 0.01$) by the F-MAX test, the mean values between each pair of groups were compared using the Behren-Fisher t-Test. Dunnett's test and the Behren-Fisher t-test were conducted at the 0.05 and 0.01 two-sided risk levels.

QUAZEPAM CARCINOGENICITY STUDY IN HAMSTERS - 18 MONTHS

672 hamsters were randomly divided into 4 dose groups of 56 males and 56 females each and into a control group of 112 males and 112 females. Doses were 0, 3, 20, and 120 mg/kg/day for quazepam and 120 mg/kg/day for diazepam.

The doses selected were based on the results of a one-month pilot study which used doses up to 250 mg/kg/day. Elevated transaminase and liver weights at the 250 mg level were apparently part for the reason for limiting the high dose in this 18 month study to 120 mg/kg/day. The dose levels in this 18 month study were approxiamtely 5, 39, and 200 times the proposed maixmum human dose of 0.6 mg/kg/day. The drugs were administered by food admixture. Measurement of plasma levels of a major metabolite of quazepam indicated that the drug was absorbed at all doses.

The control, diazepam, LD and MD treated males survived 18 months of dosing (11 to 36 survivors per group); 120 mg/kg (HD) males were killed after 73 weeks of dosing (13 survivors) and all groups of surviving females were killed after 57 weeks of dosing at which time 14 to 26 hamsters remained in each group. Of the initial number of hamsters in each group, 50% survived for as long as 55 to 66 weeks for males and 46 to 55 weeks for females. Most of the interim deaths occurred after 30 weeks of dosing and were associated with enteritis.

Treated animals showed increased body weight and food consumption for up to a year of dosing as well as incidence if ataxia, alopecia, tremors, teeth chattering, and increased activity when compared to controls. Clinical chemistry and hematological values were not affected by treatment. No increase in tumors was observed in hamsters given either diazepam or quazepam. Tables showing the distribution of tumor types (both neoplastic and nonneoplastic) are reproduced below.

Spontaneous tumors which occurred appeared with the greatest frequency in the adrenal gland and intestine. There was no compound related increase in the incidence of tumors or change in tumor malignancy. The most frequently occurring tumor was the cortical adenoma, which is a common tumor in the hamster. These tumors as well as intestinal adenocarcinomas (a tumor often associated with enteritis in hamsters) were found to occur equally between sexes and were distributed among treated and control groups in random fashion. The following microscopic changes were observed and were believed to be compound-related, occurring primarily at the high dose level of either quazepam or diazepam: (liver) hemorrhagic necrosis, hepatocellular regeneration, hepatocytomegaly, cytoplasmic pigmentation, extramedullory hematopoiesis. Also observed were gallbladder edema, subcapular spindle cell hyperplasia and cortical pigmentation in the adrenal gland, and atrial thrombosis in the heart. The incidence of these findings was variable but statistically significantly greater at high dose than in controls.

The general conclusion is that quazepam is not carcinogenic in hamsters at doses ranging from 5 to 200 times the maximum proposed human dose of 0.6 mg/kg. The following pages contain the sponsor's tables of tumor incidence and type.

18-MONTH ONCOGENITY STUDY OF SCH 16134 IN HAMSTERS

FREQUENTLY OCCURRING NON-NEOPLASTIC LESIONS

LESION		CONTROL	150 mg/kg DIAZEPAM	SCH 16134 (mg/kg) 3	20	120
HEPATOCYTES/PIGMENT						
	M	2/112	56/56[a]	45/54[a]	55/56[a]	51/56[a]
	F	4/112	54/56[a]	10/56[a]	22/56[a]	53/56[a]
HEMORRHAGIC NECROSIS						
	M	0/112	15/56[a]	2/54	6/56[a]	26/56[a,d]
	F	1/112	5/56[b]	1/56	2/56	21/56[a,c]
HEPATOCELLULAR REGENERATION						
	M	0/112	7/56[a]	3/54[b]	6/56[a]	15/56[a]
	F	1/112	0/56	0/56	2/56	11/56[a,c]
HEPATOCYTOMEGALY						
	M	4/112	26/56[a]	7/54[b]	15/56[a]	48/56[a,c]
	F	5/112	14/56[a]	7/56	3/56	25/56[a,d]
EDEMA OF GALLBLADDER						
	M	5/103	9/54[b]	7/45[b]	5/51	8/51[b]
	F	4/104	2/54	0/50	2/50	12/49[a,c]
ADRENAL HYPERPLASIA						
	M	62/112	39/55[a]	24/55	26/55	41/56[b]
	F	14/112	30/56[a]	1/56	8/55	34/55[a]
ADRENAL PIGMENT						
	M	67/112	44/55[a]	39/55	35/55	48/56[a]
	F	15/112	37/56[a]	1/56	4/55	43/55[a]
ATRIAL THROMBOSIS						
	M	13/112	17/56[a]	8/55	7/56	25/56[a]
	F	30/112	9/56	12/56	8/56	19/56[d]
EXTRAMEDULLARY HEMATOPOEISIS						
LIVER	M	7/112	9/56[b]	5/54[b]	12/56[a]	19/56[a,d]
	F	1/112	4/56[b]	4/56[b]	7/56[a]	13/56[a,d]
SPLEEN	M	41/112	21/56	19/54	28/56	30/56[b]
	F	46/112	21/56	23/56	18/56	29/56

a = $P \leq 0.01$ compared to Control

b = $P \leq 0.05$ compared to Control

c = $P \leq 0.01$ compared to Diazepam

d = $P \leq 0.05$ compared to Diazepam

Statistical evaluation of data was performed by Schering Corporation, Lafayette, NJ.

NEOPLASTIC LESIONS IN HAMSTERS

Organ/ Tumor Type	Sex	Incidence/# Observed Animals Control	Diazepam (120 mg/kg)	Quazepam (mg/kg) LD (3)	MD (20)	HD (120)
Spleen						
malignant lymphoma	M	4/112	1/53	2/53		
	F	3/111			1/55	
reticulam cell screen	F	2/111	3/35	1/35		2/52
Pancreas						
islet cell adenoma	M		2/54			
Esophagus						
malignant lymphoma	M	2/10				
Lung						
malignant lymphoma	M	6/12				
	F	2/111				
Liver						
malignant lymphoma	M	5/112				
	F	3/111				
reticulam cell sarcoma	M	1/112				
	F		2/56			
Ileum						
malignant lymphoma	M	2/103		1/44		
adenocarcinoma	M	2/103				
Cecum						
adenocarcinoma	M	1/108	2/53	3/50	4/54	1/55
	F	2/105			2/53	4/54
Mesenteric Lymph Node						
metastatic adenocarcinoma	F	4/105	1/53	1/42	4/52	2/49
Bone Marrow (sternum)						
malignant lymphoma	M	6/111				
Lymph Node (cervical)						
malignant lymphoma	M	5/103				
reticulam cell sarcoma	F	1/108	2/55			
Bone (femur)						
malignant lymphoma	M	5/110				
Adrenal						
cortical adenoma	M	15/112	11/55	15/55	9/55	9/56
	F	5/112	2/56		2/55	5/55
cortical carcinoma	M	1/112		1/55	1/55	1/56
malignant lymphoma	M	1/112	1/55		1/55	
pheochromocytoma	M					3/56

NDA 18-708

Quazepam Carcinogenicity Study in Mice - 18 Months

Animal: CD-1 albino mice

Dose: 0, 30, 60, 120 mg/kg p.o. daily

and sec per group: 55M, 55F tested. Control = 105M, 105F

Duration: 18 months intended with males getting an extra 13 weeks

The mouse was selected as the test species in this study because pharmacological activity and proof of absorption of drug by mice had been demonstrated and the mouse is an accepted animal model for carcinogenicity studies.

Survival

Most of the intercurrent deaths occurred after 52 weeks of dosing.

		Dose mg/kg			
		0	30	60	120
males	percent mortality: at 52 weeks	9	14	20	8
	percent mortality: at 91 weeks	57	62	50	44
females	percent mortality: at 52 weeks	5	6	2	4
	percent mortality: at 79 weeks	42	52	52	62

The mice were observed daily for changes from normal physical appearance and behavior. Each mouse was palpated weekly for tissue masses. Plasma concentrations of quazepam were monitored during the study. Microscopic examination was performed on all tissues from mice that died during the study, from all control and high dose mice at termination, and on selected tissues from low and mid-dose mice.

Refer to the table below for incidence of tumors. Postmortem examination of animals which died or were sacrificed during this study or at the terminal necropsy revealed no drug-related changes. Nocules and masses occurred most frequently in the lungs, liver, kidneys, and lymph nodes, and were equally distributed across all groups. The most common incidental changes observed in all groups included: emaciation, inflammatory changes, congestion, atrophy or dilatation of organs, uroliths in the urinary tract, alopecia, and bone fracture.

No-drug related effect upon total tumor incidence or the number of tumor bearing mice was observed. The most frequently observed tumors were adenoma of the liver and lung, and tumors of lymphoreticular tissue. Adenoma of the liver occurred more frequently in males. Tumors of lymphoreticular tissue occurred more frequently in females and adenomas of the lung were equally distributed between the sexes. No study was made concerning the effect of the drug on latency of tumor appearance. There was discussion of which types of observed tumors are actually common to the aging mouse, such as amyloid in the zona reticulosis of the adrenals, the villi of the intestine, the renal glomerule, and around the hepatic veins of all groups including the control.

An increase in the incidence of amyloid in adrenals, G.I. tract, and kidneys of the HD males was observed (see table below). While there was an increase in the incidence of amyloid in the liver of MD females, there was no increase seen in the HD group. It is difficult to attach any toxicological signficance to this finding. There did seem to be a dose-related increase in yellowish brown pigment in the cytoplasm of hepatocytes of treated mice. Considering all of the evidence of this study it appears that quazepam is not oncogenic in the mouse.

TABLE 79029

18-MO[NTH] [ONCOGENICITY] STUDY OF SCH 16131 IN MICE

INCID[ENCE] OF AMYLOID AN[D] YELLOW-BROWN PIGMENT

OBSERV[ATIONS]	DOSE LEVELS (mg/kg) 0 M	0 F	30 M	30 F	60 M	60 F	120 M	120 F
ADRENA[LS]								
Amyl[oidos]is	6/99	47/98	3/50	26/50	6/50	20/49	14/50*	26/50
Dege[neration], brc	72/99	21/98	30/50	17/50	12/50	10/49	1/50	10/50
Prol[iferation], sub[capsular]	61/99	72/98	24/50	28/50	18/50	25/49	27/50	24/50
G.I. T[RACT], AMYLOIDOSIS								
Duod[enum]	1/98	38/97	2/50	20/48	2/49	19/48	9/49*	25/49
Ileu[m]	1/99	41/97	9/50	27/49	8/49	20/49	16/49*	23/49
Jeju[num]	2/99	41/97	8/50	33/49	11/49	33/49	17/49	31/49
KIDNEY								
Amyl[oidos]is	16/100	47/98	4/50	29/50	6/50	27/50	14/50*	28/50
LIVER								
Amyl[oidos]is	6/100	17/98	6/50	16/50	1/50	19/50*	2/50	16/50
Yell[ow-]brown Pig[ment]	25/100	26/98	16/50	15/50	23/50*	23/50*	42/50*	31/50*

* Stat[istic]ally significant p≤0.05.

LE 1
SOUTH MICROGENICITY [illegible] OF SCH 1611? IN MICE

79029

DAILY TABLE: [illegible]

C CE /KG)	NO. MICE /GROUP/ SEX	TOTAL UNSCHED. DEATHS MALES	FEMALES	WEEK OF 50% MORTALITY MALES	FEMALES	NO. KILLED AT TERM. NECROPSY MALES	FEMALES	WEEK OF TERM NECROPSY MALES	FEMALES	% SURVIVORS TERM. NECROPSY MALES	FEMALES	% MORTALITY UNSCHED. DEATHS MALES	FEMALES
0 reated)	100	57	42	89	79[b]	43	58	91	79	43	58	57	42
30 H 1611+)	50	31	26	84	77	19	24	91	79	38	48	62	52
60 H 1611+)	50	25	26	90	75	25	24	91	79	50	48	50	52
120 H 1611+)	50	22	32	91[c]	68	20	18	91	79	56	36	44	64

es not include [illegible] to study absorption of test substance
s mortality at [illegible]
s mortality at [illegible]

TABLE 7
18-MONTH ONCOGENICITY STUDY OF SCH 16134 IN MICE

DISTRIBUTION OF TUMORS IN MICE: PREFACE

CLASSIFICATION OF NEOPLASMS OF LYMPHORETICULAR TISSUE

The histopathologic classification of Dunn (J. Nat. Cancer Inst. 14, 1281, 1954) was used for the neoplasias of the lymphoreticular tissue.

Lymphocytic neoplasms refer to neoplasms composed of uniform cells resembling normal lymphocytes but at times showing clear indented vesicular nuclei, prominent nucleoli and pale blue cytoplasm.

Neoplasm Type A: The reticulum-cell neoplasms Type A are composed of a single cell type, the monocyte or histiocyte. This cell shows various size and degree of phagocytic activity characterized by a foamy appearance and by the presence of phagocytized debris or hemosiderin.

Neoplasm Type B: The reticulum-cell neoplasms Type B have a pleomorphic structure showing basophilic mononuclear cells intermingled with plasma cells, a few granulocytes and occasional multinucleated cells and eosinophils. Dunn refers to this neoplasm as the "Hodgkin's-like lesion."

Neoplasm Type C: The reticulum-cell neoplasms Type C are composed of pale-staining fusiform cells arranged in masses or trabeculae bordered by lymphocytes. These features resemble a chronic granulomatous process in man such as Boeck's sarcoid or tuberculosis without, however, asteroid bodies, necrosis or multinucleated cells.

TABLE 7
18-MONTH ONCOGENICITY STUDY OF SCH 16134 IN MICE

DISTRIBUTION OF TUMORS IN MICE: WEEKS 1 - 91

OBSERVATIONS	DOSE LEVELS (mg/kg)							
	0		30		60		[illegible]	
	M	F	M	F	M	F	M	F
ADRENALS								
Adenoma	2							
BONE								
Hemangiosarcoma					1			
Osteoma		1						
DUCTUS DEFERENS								
Hemangioma			1					
EPIDIDYMIDES								
Lipoma	1							
HARDERIAN GLANDS								
Adenoma	2							
JEJUNUM								
Lipoma		1						
LACRIMAL GLANDS								
Adenoma						1	1	
LIVER								
Adenoma	13		3	1	5	2	9	2
Carcinoma	1							
Hemangioma		1				1		
[illegible]								
Adenocarcinoma	1		1					
Adenoma	13	7	6		4	1	4	
[illegible]								
Hemangiosarcoma (Spleen)			1	1		1	1	
[illegible] Granulocytic	1	1						
Lymphocytic Neoplasm		5	1	5		3	1	1
Neoplasm Type A	3	3		2		1		
Neoplasm Type B		6	1	1		2	1	1
Neoplasm Type C								1

TABLE 7
18-MONTH ONCOGENICITY STUDY OF SCH 16134 IN MICE

DISTRIBUTION OF TUMORS IN MICE: WEEKS 1 - 91

OBSERVATIONS	DOSE LEVELS (mg/kg)							
	0		30		60		120	
	M	F	M	F	M	F	M	F
MAMMARY GLAND								
Carcinoma		1						
MESOMETRIUM								
Lipoma								1
OVARIES								
Carcinoma				1				
Cystadenoma				2				
Granulosa-Leydig Cell Tumor		12						3
Thecoma								1
PANCREAS								
Adenoma		1						
PITUITARY								
Adenoma		2						
RECTUM								
Adenomatous Polyp								1
SKIN, SUBCUTANEOUS TISSUE								
Adenoma, Sebaceous						1		
Hibernoma	1							
TAIL								
Fibrosarcoma				1				
THYROID								
Adenoma	1							
UTERUS								
Carcinoma		4		1				
Leiomyoma		1		1				
Leiomyosarcoma		2						
URINARY BLADDER								
Carcinoma	1							
Papilloma	3		1					

TABLE 7
13-MONTH ONCOGENICITY STUDY OF SCH 16134 IN MICE

DISTRIBUTION OF TUMORS IN MICE: WEEKS 1 - 91

OBSERVATIONS	DOSE LEVELS (mg/kg)							
	0		30		60		[illegible]	
	M	F	M	F	M	F	M	F
Number of Tumors	45	54	16	16	10	13	17	28
Tumor Bearers	40 40%	41 41%	13 26%	15 30%	9 18%	13 26%	16 32%	25 50%
Number of Animals	100	98	50	50	50	50	50	50

TABLE 7
18-MONTH ONCOGENICITY STUDY OF SCH 16134 IN MICE

DISTRIBUTION OF TUMORS IN MICE: SCHEDULED SACRIFICES

OBSERVATIONS	DOSE LEVELS (mg/kg)							
	0		30		60		[illegible]	
	M	F	M	F	M	F	M	F
ADRENALS								
Adenoma	2							
DUCTUS DEFERENS								
Hemangioma			1					
EPIDIDYMIDES								
Lipoma	1							
HARDERIAN GLANDS								
Adenoma	2							
JEJUNUM								
Lipoma		1						
LACRIMAL GLANDS								
Adenoma						1		1
LIVER								
Adenoma	9		1	1	2		6	1
LUNGS								
Adenocarcinoma			1					
Adenoma	10	1	3		2	1	3	5
LYMPHORETICULAR SYSTEM								
Hemangiosarcoma (Spleen)						1		
Leukemia, Granulocytic								
Lymphocytic Neoplasm								
Neoplasm Type A								
Neoplasm Type B								
MESOVARIUM								
[illegible]								
[illegible]								
[illegible]								
[illegible]								
[illegible]								
[illegible]								
Adenomatous Polyp								

TABLE 7
18-MONTH ONCOGENICITY STUDY OF SCH 16134 IN MICE

DISTRIBUTION OF TUMORS IN MICE: SCHEDULED SACRIFICES

OBSERVATIONS	DOSE LEVELS (mg/kg)							
	0		30		60		[illegible]	
	M	F	M	F	M	F	M	F
SKIN, SUBCUTANEOUS TISSUE								
Adenoma, Sebaceous				1				
Hibernoma	1							
TAIL								
Fibrosarcoma			1					
THYROID								
Adenoma	1							
UTERUS								
Carcinoma		2		1				
Leiomyoma		1		1				1
Leiomyosarcoma		1						
URINARY BLADDER								
Papilloma			1					
Number of Tumors	27	26	9	5	4	5	11	14
Tumor Bearers	24	23	7	4	4	5	10	11
	56%	35%	35%	16%	16%	22%	36%	61%
Number of Animals	43	66	20	25	25	23	28	18

TABLE 7
18-MONTH ONCOGENICITY STUDY OF SCH 16134 IN MICE

DISTRIBUTION OF TUMORS IN MICE: UNSCHEDULED DEATHS OR SACRIFICE

OBSERVATIONS	DOSE LEVELS (mg/kg) 0 M	0 F	30 M	30 F	60 M	60 F	[illegible] M	[illegible] F
BONE								
Hemangiosarcoma					1			
Osteoma		1						
LIVER								
Adenoma	4		2		3	2	3	1
Carcinoma	1							
Hemangioma		1				1		
LUNGS								
Adenocarcinoma	2							
Adenoma	3	3	3		2		1	1
LYMPHORETICULAR SYSTEM								
Hemangiosarcoma (Spleen)				1			1	
Leukemia, Granulocytic	2	1						2
Lymphocytic Neoplasm		4	1	5		3	1	6
Neoplasm Type A	2	3		2				1
Neoplasm Type B		6	1	1		2		1
Neoplasm Type C								1
MAMMARY GLAND								
Carcinoma				1				
OVARIES								
Cystadenoma								
Interstitial-Leydig Cell Tumor								
[illegible]								
Adenoma				1				
[illegible]								
[illegible]				-				
UTERUS								
Carcinoma				2				
Leiomyosarcoma				1				
URINARY BLADDER								
Carcinoma	1							
Papilloma	3							

TABLE 7
18-MONTH ONCOGENICITY STUDY OF SCH 16134 IN MICE

DISTRIBUTION OF TUMORS IN MICE: UNSCHEDULED DEATHS OR SACRIFICES

OBSERVATIONS	DOSE LEVELS (mg/kg) 0 M	0 F	10 M	10 F	50 M	50 F	100 M	100 F
Number of Tumors	18	28	7	11	6	8	6	14
Tumor Bearers	16 28%	18 56%	6 20%	11 44%	5 20%	8 30%	6 27%	14 44%
Number of Animals	57	32	30	25	25	27	22	32

NCA 18-708

Sponsor's Mutagenicity Report

Quazepam was tested, over a range of concentrations for 2 g/ml to 200 g/ml, in the L5178YTK+/- Mouse Lymphoma Mutagenesis assay with and without exogenous metabolic activation (5-9) by Arocior induced rat liver microsomes. Non-activated cultures were cloned over a range of 11 to 200 g/ml of quazepam. Several of the cultures exhibited mutant frequencies which were two-fold greater than solvent controls. The results of this study show that the test article may have induced a positive response. For the 5-9 activated cultures cloned over a concentration range of 2-47 g/ml, only the two highest treated cultures 36 and 47 g/ml showed mutant frequencies which were greater than twice control. The Ames test was negative.

OVERALL SUMMARY AND EVALUATION

Quazepam is a hypnotic agent related structurally to flurazepam and diazepam. The sponsor proposes that the drug be marketed for the treatment of all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings. The drug is to be marketed in 15 and 30 mg tablets with the daily recommended dosage of 0.6 mg/kg or 30 mg daily for the 50 kg human. Relevant animal studies performed include acute and chronic toxicity in the hamster and squirrel monkey, reproduction studies using the mouse and rabbit, carcinogenicity studies in the mouse and hamster, and other appropriate studies of pharmacological activity, drug metabolism, mutagenicity, etc.. Pilot studies showed quazepam to be largely inactive in the rat because, although well absorbed orally, quazepam is rapidly metabolized and excreted in the rat. Thus, tissue levels of the drug sufficient to cause pharmacological effect in that species cannot be achieved. The hamster was selected for the long term rodent testing because that animal responded to the toxicologic and pharmacologic properties of quazepam and because studies showed that the hamster metabolized quazepam in a manner similar to that found in man.

The main behavorial effects of quazepam in animals are drowsiness and sedation. Quazepam was found to be twice as potent as flurazepam and half as potent as lorazepam in hypnotic activity measured using the eye closure test in monkeys. Studies of the dependence potential of Quazepam produced results which suggest a profile similar to that of marketed benzodiazepine (this is further elaborated upon in a consulting review from the Drug Abuse Unit). Like diazepam and flurazepam, quazepam potentiated the ethanol-induced loss of righting reflex in mice. Quazepam produced no significant changes in blood pressure, heart rate, or EKG in the unanesthetized dog while doses (60 mg/kg) large enough to cause ataxia and sedation were used.

Quazepam is well absorbed by the mouse, rat, hamster, squirrel, monkey, and man when given orally. It is almost totally metabolized and extensively so on first pass. Four pharmacologically active metabolites have been identified. The plasma half-life of quazepam is about 40 hours in man. Quazepam penetrates the placental barrier, and does so more readily near term than at embryonic states. Quazepam and its metabolites are excreted in urine and feces, mostly within 24 hours of administration. The drug is a weak inducer of hepatic drug metabolizing enzymes in the hamster.

Signs of acute toxicity of quazepam in animal studies included hypoactivity, deep respiration, ptosis, head shaking, ataxia, and straub tail in mice. Long term toxicity studies were performed using the hamster (1 year) and squirrel monkey (1 year).

The namster study used doses of drug which ranged from 5 to 200 times the maximum proposed human dose of 0.6 mg/kg (i.e., 0, 3, 20, 120 mg/kg/day). One group of hamsters was treated with diazepam (120 mg/kg) for comparison. Mortality among the hamster was evenly divided between dosed and control groups, and was attributed to enteritis, atrial thrombosis, and heart failure, or renal amyloidosis and uremia. The conditions were regarded as spontaneous and not drug related. Both diazepam and quazepam elicited ataxia, alopecia, tremors, and hyperactivity at the high dose level. While neither drug altered water consumption, both drugs were associated with enhanced body weight and food consumption in the HD males. The drugs did not alter hematology or clinical chemistry values. Bile retention was the only significant finding by histopathology and occurred at HD for both drugs. The dose range employed was sufficient both to demonstrate evidence of toxicity and allow for acceptable long term survival of the animals.

The requirement for long term testing in a non rodent test animal was approached with a one year study using the squirrel monkey. Doses of 2, 10, and 50 mg/kg were employed as was a 50 mg/kg diazepam control dose. The quazepam doses were 3, 17, and 83 times the proposed maximum human dose. Both drugs produced sedation, somnolence, ataxia, and tremors. No compound related effects could be determined from hematology, blood chemistry, and urinalysis. The doses of drug employed were sufficient to allow adequate survival rates while still showing pronounced pharmacological effect.

Reproduction studies were conducted using the mouse and rabbit. Doses were used in the Segemnt I mouse study which correspond to 20, 60, and 180 times the proposed human dose. There was a dose-related reduction in number of pregnancies (0 at low dose, 20% at medium dose, and 30% at high dose), increase in number of embryoic deaths, increased post-implantation loss (17% at high dose versus 6.7% for control), and increased pup loss. The drug did not affect duration of gestation. Some of the pups that survived showed retarded development. The teratology study in the mouse showed some instances of retarded bone ossification which could be considered drug related, but only at the high dose. Teratology studies in the rabbit did not reveal any evidence that ~~flurazepam~~ Quazepam would be a teratogen in that species.

Carcinogenicity studies were performed using the hamster and the mouse. Incidence of lesions were analyzed using Fisher's Exact test , F-MAX, ANOVA, Dunnett's test, and the Behren-Fisher t-test. In the mouse, nodules and masses occurred most frequently in the lungs, liver, kidneys, and lumph nodes, and were equally distributed across all groups. No drug-related effect upon total tumor incidence or the number of tumor-bearing mice was observed. The most frequently observed tumors were adenoma of the liver and lung, and tumors of lymphoreticular tissue. Taken as a whole, the mouse data do not present evidence for quazepam carcinogenicity in that species. The 18 month carcinogenicity study using the hamster, employed doses of quazepam approximately 5, 33, and 200 times the proposed maximum human dose. Of the initial number of hamsters in each group, half of the males survived to 55-56 weeks while half of the females survived to 46-55 weeks. No increase in tumors was observed in hamsters given either diazepam and quazepam. Spontaneous tumors which occurred appeared with the greatest frequency in the adrenal gland and intestine. There was no compound-related increase in the incidence of tumors or change in tumor malignancy. The most frequently occurring tumor was the cortical adenoma, a common tumor in the hamster. These tumors as well as intestinal adenocarcinomas (a tumor often associated with enteritis in hamsters) were found to occur equally between sexes and were distributed among treated and control groups in random fashion. The data generally did not support a role for quazepam as a carcinogen in the hamster.

RECOMMENDATIONS:

I recommend that the application be approved from the preclinical animal toxicity viewpoint. In my evaluation of the toxicity data I could not find grounds for refusing to approve. The application appears to contain adequate preclinical tests by all means reasonably applicable to show whether or not the drug is safe to use under the conditions in the labeling. The proposed labeling, in my view, is not false or misleading regarding preclinical study results.

Robert Hollenbeck

Robert Hollenbeck, Ph.D.
Reviewing Pharmacologist

Orig. NDA 18-708
HFN-120
HFN-120/RHollenbeck
JContrera/6-13-85
HFN-180
HFN-102/Glocklin
F/T:GD/6-18-85
Doc. 0095f

N 18708 Bio

NDA
18708

Bio Rvs

Quazepam (Dormalin) Tablets, 7.5 mg
NDA 18-708
Reviewer: Pratapa Prasad
[redacted]

Schering Corporation
Kenilworth, NJ
Date of Submission:
August 6, 1986

MAR 20 1990

Review of an NDA

The Agency approved quazepam 15 mg tablets on December 27, 1985. The product's labeling indicates that Dormalin 15 mg tablet can be scored. Based on this fact, the firm submitted a supplement seeking approval of a 7.5 mg strength tablet on June 17, 1986 stating "since the approved NDA allowed for the 15 mg dose to be reduced to 7.5 mg dose via a half of a scored tablet, this supplemental application insures the accessibility of the reduced dose in a 7.5 mg tablet" (see Attachment I). Later, on August 6, 1986 (present submission) the firm submitted an addendum to the June 17, 1986 supplement. The present submission contains a dose proportionality study, which had been provided in the original NDA (April 2, 1982), comparing 7.5, 15, and 30 mg tablets of quazepam. The Division of Biopharmaceutics had reviewed the results of the study (April, 1986) and concluded that quazepam showed dose proportionality between 7.5 and 30 mg doses based on AUC results.

It should be noted that the formulation for the 7.5 mg Dormalin tablet used in the dose proportionality study was identical to that of the 15 mg tablet except for the active ingredient whereas the 7.5 mg tablet proposed for marketing contains half of the active and inactive ingredients of the 15 mg tablet (see Tables 1 and 2). It appears that a biostudy was never conducted using the 7.5 mg to be marketed formulation nor was a waiver request submitted to the Agency by the firm; however, the 7.5 mg Dormalin tablet was approved by the Agency as of February 26, 1987.

Dissolution: After a review of the data in the original NDA, the Division of Biopharmaceutics provided the following interim dissolution specifications for Dormalin tablets:

900 ml of 40% ethanol in water at 37 ^{0}C, Apparatus II at 50 RPM;
Q = [redacted]

Additionally, the sponsor was requested and it was agreed that the firm should explore the applicability of aqueous buffer media (non-alcoholic media) with or without solubilizing agent(s) and generate pH- related dissolution profiles for this product. In fact, the firm was requested to provide the above information within 180 days after the December 27, 1985 approval letter. The Division of Biopharmaceutics has not yet received such information from the sponsor.

Recommendation:

The Division of Biopharmaeutics recommends that the firm, as previously committed, should submit dissolution results for Dormalin tablets using aqueous and different pH media ~~within 60 days after receiving this recommendation~~ for establsihing dissolution method and specification. After the dissolution specification is established for Dormalin tablets, the firm should submit comparable dissolution data on Dormalin 7.5 mg and 15 mg tablets to meet the requirements of the Division of the Biopharmaceutics. The comparative test should be from at least 3 full scale production lots using 12 tablets/lot per each strength.

Please forward the above Recommendation to the sponsor.

Pratapa P. Bas 3/19/90
Pratapa P. Prasad, Ph.D.
Pharmacokinetic Evaluation Branch

RD Initialed by Raman Baweja, Ph.D. March 15, 1990

FT Initialed by Paul L. Hepp, Pharm.D. [illegible]

cc: NDA 18-708, HFD-120, HFD-344 (Turner), HFD-426 (Prasad), Chron, Division, Drug, Reviewer, and HFD-19 (FOI) files.

...IAL ... 18-708 REF. NO S-002 CE

NDA SUPPL FOR Additional TABLET STRENGTH

FPL

APPLICATION FORM

1. INDEX

SCHERING CORPORATION

CALLOPING HILL ROAD KENILWORTH, N.J. 07033

CABLES: SCHERING KENILWORTH

TELEX: 138316
138280

TELEPHONE: (201) 558-4000

S-001

ATTACHMENT-I

June 17, 1986

Verbal Concurrence 6.27.86

Paul Leber, M.D., Director
Division of Neuropharmacological Drug Products
HFN 120, Room 10B-34
Center for Drugs and Biologics
5600 Fishers Lane
Rockville, Maryland 20857

RECEIVED
NATIONAL CENTER
JUN 18 1986
HFN-120
FOR DRUGS & BIOLOGICS

SUBJECT: Dormalin® Tablets - NDA 18-708

Dear Dr. Leber:

Submitted herewith is a supplement to our approved New Drug Application #18-708 for Dormalin® Tablets, which provides for an additional tablet strength, 7.5 mg. Since the approved NDA allowed for the 15 mg dose to be reduced to 7.5 mg dose via a half of a scored tablet, this supplemental application insures the accessibility of the reduced dose in a 7.5 mg tablet.

This supplemental application, which consists of three volumes, has been prepared according to the new format as described in section 314.50 of the new NDA regulations. As required, we are providing an archival copy (three volumes) and one review copy of the Chemistry, Manufacturing and Controls technical information. Also as directed in the Guidelines, we are providing 12 copies of the final printed labeling in a separate envelope inserted in the "Samples and Labeling" section of archival volume 3.

Please note that the contents of this supplemental New Drug Application are identified on the back of the attached application form.

We look forward to your prompt review and approval.

Sincerely,

Patricia L. Thomas /for

Alexander R. Giaquinto, Ph.D.
Vice President
Regulatory Affairs

PT:ltr
Enclosures

USED IN DOSE PROPORTIMALITY STUDY.

TABLE 1

QUAZEPAM TABLET FORMULATIONS

Ingredients	7.5 mg Batch No. 10392-131 FMR No. 796660-02 Batch Size: [redacted] mg/tablet	15 mg Batch No. 11194-75 FMR No. 796910-02 Batch Size: [redacted] mg/tablet	30 mg Batch No. 11194-98 FMR No. 797340-02 Batch Size: [redacted] mg/tablet
Quazepam, Micronized	7.50	15.00	30.00

1. Composition and Description: Table 2

A. Composition:

The components in the 7.5 mg tablets are identical to those in the approved 15 mg tablet (NDA 18-708). The relative percentage composition of each component are also identical.

Component	7.5 mg* Tablet	15 mg Tablet
Quazepam, Micronized	7.5	15.0

B. Drug Product Description:

The dosage form is a light-orange, slightly white-speckled, biconvex capsule shaped tablet scored on one side and engraved with the NDC code or strength on both sides of the score, and DORMALIN or the name "Shering" on the other side of the tablet.

M E M O R A N D U M

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drugs and Biologics
Office of Drug Standards

[redacted]

DATE : DEC 13 1985

TO : Paul Leber, M.D.
Director,
Division of Neuropharmacological Drug Products (HFN-120)

FROM : Jerome P. Skelly, Ph.D.
Acting Director,
Division of Biopharmaceutics (HFN-220)

SUBJECT: Amendment to Biopharmaceutics Recommendation of Approval
Quazepam; NDA 18-708
Schering Corporation; Submission Date: April 2, 1982

This memorandum is intended to amend the original Biopharmaceutics Recommendation of Approval dated May 4, 1983. Under "Summary of Pivotal Studies", paragraph #6 should be modified to read:

> In a crossover, open-label study, twelve healthy male volunteers received one 15 mg tablet of quazepam either at night prior to sleep or in the morning. Results indicated that the pharmacokinetics of quazepam and its major active plasma metabolites are not appreciably altered by time of administration, but bioavailability was somewhat greater when the drug was given at night. Total body clearance for the nighttime dose was about 17% less than that for the morning dose. The Cmax and AUC for quazepam and 2-oxoquazepam and the AUC for N-desalkyl-flurazepam were consistently greater following the nighttime dose.

Paragraph #7 should read:

> Four healthy, nonpregnant, lactating women volunteers ingested one 15 mg quazepam tablet. Quazepam and its two major active metabolites were found to be excreted in breast milk. Levels of quazepam in breast milk were consistently higher than corresponding plasma levels during the first 12 hr postdosing, and similarly elevated values for 2-oxoquazepam were found during the first eight hours. Breast milk levels of N-desalkylflurazepam were less than one-tenth that of plasma levels at corresponding times. During 48 hours following this single dose, parent and metabolites recovered in breast milk amounted to 0.11% of the quazepam dose.

Regarding Dissolution:

Until the potential for use of aqueous media has been explored, use of an ethanolic dissolution medium is acceptable in an interim basis. The dissolution testing is to be conducted in 900 ml of 40% V/V ethanol in water (37°C) using USP Paddle apparatus operated at 50 rpm. The test product should meet the following specification:

Q=[redacted] in [redacted] minutes

Jerome P. Skelly

Prepared by Karen B. Oseekey
RD Initialed by Paul L. Hepp, Pharm.D.
FT Initialed by C.T. Viswanathan, Ph.D. CTV 12.12.85

cc: HFN-120, HFN-220(2), HFN-226(Oseekey), Chron, Drug, and FOI Files

KBO:smj:kek:[redacted] (12/12/85)

Quazepam
Dormalin
15 mg tablet
NDA 18-708
Reviewer: Karen B. Oseekey
Wang #[redacted]
0-1

Schering Corporation
Bloomfield, NJ
Submission Date:
November 25, 1985

DEC 6 1985

Review of Firm's Responses to Approvable Letter

Schering Corporation has responded positively to the Agency's approvable letter dated August 30, 1985 regarding the request of the Division of Biopharmaceutics for Phase IV dissolution testing. The firm has commited to examine the use of aqueous dissolution media and will explore the applicability of aqueous buffers or solubilizing agent. They will also generate a pH-solubility profile. Until the applicability for an aqueous media has been established, the firm will continue to use an ethanol media according to the parameters and specification outlined in the Agency letter. This commitment is agreeable to the Division of Biopharmceutics.

Karen B. Oseekey
Pharmacokinetics Evaluation Branch

RD Initialed by Martin K. Yau, Ph.D. for G. Hepp
FT Initialed by CT Viswanathan, Ph.D. CTV dec 6, 1985

cc: NDA 18-708 Orig., HFN-120, HFN-226(Oseekey), Drug, Chron, and FOI files.

KBO:smj:[redacted]12-03-85

M E M O R A N D U M

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drugs and Biologics
Office of Drug Standards

DATE : September 25, 1985

TO : Paul Leber, M.D.
Director, Division of Neuropharmacological Drug Products
HFN-120

FROM : Jerome P. Skelly, Ph.D.
Acting Director, Division of Biopharmaceutics
HFN-220

SUBJECT: Amendment to Biopharmaceutics Recommendation of Approval
Quazepam; NDA 18-708
Schering Corporation; Submission date: April 2, 1982

This memorandum is intended to amend the original Biopharmaceutics Recommendation of Approval dated May 4, 1983 (copy attached). Under "Summary of Pivotal Studies", paragraph #1 should be modified to read:

Following oral administration of a solution of 25 mg ^{14}C quazepam to six healthy male volunteers, the drug was rapidly and extensively absorbed, distributed, metabolized and slowly excreted in the urine and feces. The drug was absorbed with a rate constant (ka) of 2.2 hr^{-1} for total radioactivity; the Cmax of total radioactivity was reached at 1.8 hours (Tmax). The dose was extensively absorbed as indicated by the low level of radioactivity found in feces during the first 48 hours (approximately 13% of the administered dose). Following peak levels, the plasma radioactivity declined with mean disposition half-lives of 1.9 hours for the alpha-phase and 75.6 hours for the beta-phase. The mean AUC (0-120 hr) of radioactivity was 11402.3 hr x ng/ml

The unchanged quazepam, 2-oxoquazepam (Sch 15725, formed from quazepam by exchange of oxygen for sulfur), N-desalkylflurazepam (Sch 17514, subsequently formed by dealkylation of 2-oxoquazepam), and conjugated 3-hydroxy-2-oxoquazepam (conjugated 23324) accounted for most of the plasma radioactivity.

The Cmax of quazepam (148.0 ng/ml) was reached at 1.5 hours (Tmax). The initial distribution half life ($t_{1/2}$ alpha) was 1.7 hours and terminal half life ($t_{1/2}$ beta) was 39.3 hours. The AUC (0-120hr) of quazepam (714.6 hr x ng/ml) was only about 6% of the total radioactivity. This smaller AUC along with a large volume of distribution (Vd=2.2 l/kg) and total body clearance (TBC = 591 ml/min) suggested extensive distribution and metabolism of quazepam.

The formation of 2-oxoquazepam was rapid with a rate constant (km) of 2.2 hr^{-1}; the Cmax (45.6 ng/ml) was reached at 1.6 hours (Tmax). The disposition half-lives (initial $t_{1/2\ alpha}$ =2.9 hr; terminal $t_{1/2\ beta}$ =40.2 hr) were comparable to those of quazepam. The AUC (0 to 120 hr) of 2-oxoquazepam was 438.3 hr x ng/ml.

The km of N-desalkylflurazepam (0.8 hr^{-1}) was somewhat lower than that of 2-oxoquazepam; the Cmax (40.9 ng/ml) was reached at 14 hours (Tmax). The disposition half-lives (initial $t_{1/2\ alpha}$ = 27.8 hr; terminal $t_{1/2\ beta}$ =69.5 hr) were much longer than those of its precursor, 2-oxoquazepam. The $t_{1/2\ Beta}$ of N-desalkylflurazepam was comparable to that of the total radioactivity; the AUC (0 to 120 hr) was 3323.5 hr x ng/ml which was considerably higher than that of unchanged quazepam or 2-oxoquazepam.

Conjugated 3-hydroxy-2-oxoquazepam accounted for most of the urinary radioactivity; other major urinary metabolites were conjugated 3-OH-N-desalkylflurazepam, conjugated N-desalkylflurazepam, and a polar TLC fraction. Small amounts of 2-oxoquazepam were also present in the urine. The urinary metabolic profile did not change appreciably as a function of time.

The elimination of the parent drug and 2-oxoquazepam from the body were essentially completed by 120 hours; the AUC (0 to 120 hours) were 94% and 93%, respectively, of the AUC infinity. The AUC (120 hour) of N-desalkyflurazepam and total radioactivity were 68% and 69% of the respective AUC infinity. This indicated that about 30% of N-desalklflurazepam and total radioactivity remained to be eliminated from the body after 120 hours.

Paragraph #3 should read:

Twelve healthy volunteers received single oral doses of 7.5, 15, and 30 mg in a crossover study. The AUC and dose data suggested a linear relationship between mean AUC and dose for all three compounds (quazepam, 2-oxoquazepam, and N-desalkylflurazepam). Although data pertaining to the 30 mg dose is not relevant to this NDA (since only a 15 mg tablet will be marketed) in some cases a 7.5 mg dose may be used in elderly or debilitated patients. This study established linear kinetics for quazepam and its two major active metabolites.

Paragraph#4 should read:

Following single-dose oral administration of one 15 mg quazepam tablet to twelve geriatric subjects aged 65-77 yrs, the drug was rapidly absorbed and extensively distributed and/or metabolised. The disposition half-lives in the distribution phase ($t_{1/2\ alpha}$) and the elimination phase ($t_{1/2\ beta}$) of quazepam were calculated to be 3.5 and 53.3, respectively. These values were slightly greater than those previously obtained from young adult subjects ($t_{1/2\ alpha}$=1.7 hrs, $t_{1/2\ beta}$=39.3 hours) but the total body clearance of quazepam in geriatric subjects (594.7 ml/min) was comparable to that observed in young adult subjects (590.8 ml/min).

The formation of 2-oxoquazepam was rapid as indicated by the large apparent formation rate constant, km (1.1 hr^{-1} vs 2.2 in young adults) with a tmax of 3.0 hrs (vs 1.6 hrs in young adults). The disposition half lives ($t_{1/2}$ alpha and $t_{1/2}$ beta) of 4.21 and 43.08 hours, respectively, were comparable to those of the parent drug and were also comparable to those observed in younger adults (2.87 and 40.16 hrs, respectively).

The disposition half-lives ($t_{1/2}$ alpha = 40.3 hrs, $t_{1/2}$ beta = 189.7 hrs) of N-desalkylflurazepam in geriatric subjects were much [illegible]er than those seen in young adult subjects (27.8 and 69.5 hrs, respe[illegible]ly). (Other investigators have reported that the elimination half-[illegible]es of the N-dealkylated metabolites of diazepam and flurazepam were much longer in the elderly than in the young). The $t_{1/2}$ beta of N-desalkylflurazepam showed a large intersubject variation ranging from [redacted] to [redacted] hours.

Paragraph #5 should read:

Twelve healthy male volunteers received single oral doses of 15 mg quazepam tablets once every 24 hours for 14 days. Quazepam was rapidly absorbed. The disposition kinetics showed that there was a rapid initial distribution phase with a half-life of 1.9 hours ($t_{1/2}$ alpha) followed by a slower terminal elimination phase with a half-life of 40.8 hours ($t_{1/2}$ beta). Steady state levels of quazepam were reached by the seventh dose as predicted from single-dose pharmacokinetics. The accumulation index (R_A), calculated for each subject from the AUC dosing interval ratio of the 7th dose to the first dose, was approximately 1.5, indicating that the steady-state levels were 50% greater than plasma levels obtained following the first dose.

2-oxoquazepam was formed rapidly from quazepam ($t_{1/2}$ km = 1.2 hr) and the disposition kinetics (initial $t_{1/2}$ alpha = 2.0 hrs, final $t_{1/2}$ beta = 43.1 hrs) were comparable to those of the parent drug. Like quazepam, steady state of 2-oxoquazepam was reached by the seventh dose. The accumulation ratio was 1.4.

N-desalkylflurazepam was formed rapidly from 2-oxoquazepam and eliminated slowly with a terminal half-life ($t_{1/2\ Beta}$) of 75 hours, which is comparable to previous single-dose data (70 hrs). Steady state of N-desalkylflurazepam was reached by the 13th dose as predicted from single-dose pharmacokinetics and the steady-state plasma levels were about five fold higher than plasma levels obtained after the first dose. Since the half-life of this metabolite is three times greater than the dosing interval, these higher steady-state concentrations were not unexpected. (Similar degrees of plasma level increase of the N-desalkyl metabolites of diazepam, flurazepam and medazepam are reported in the literature).

Jerome P. Skelly, Ph.D.

Prepared by K.B. Oseekey
RD Initialed by Paul L. Hepp, Pharm.D.
FT Initialed by C.T. Viswanathan, Ph.D. CTV

cc: HFN-120(Leber), HFN-220(Skelly, Shulman), HFN-226(Oseekey) Drug, and Chron Files

KBO:tw:smj:dea:kek:([redacted]) 9/13/85

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M E M O R A N D U M

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
National Institutes of Health

Attachment

TO : Dr. Paul Leber
Director, Division of Neuropharmacc
HFN-120

1983

FROM : Jerome P. Skelly, Ph.D.
Acting Director, Division of Biopharmaceutics
HFN-520

SUBJECT: Biopharmaceutics Summary Basis of Approval;
Quazepam; NDA 18-708
Schering Corporation; Submission date: April 2, 1982

Background:

Quazepam was developed as a hypnotic compound in the benzodiazepine family and has been shown to be an effective sedative hypnotic drug in man. Quazepam is indicated for the treatment of all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, early morning awakenings, insomnia in geriatric patients, and in those patients requiring a rapid acting hypnotic for insomnia associated with situational stress or crisis, such as that experienced prior to surgery.

Summary of Pivotal Studies:

Following oral administration of ^{14}C quazepam in solution form to six healthy adult male volunteers, the drug was rapidly and extensively absorbed, distributed, metabolized and slowly excreted in the urine and feces. The metabolic pathway following administration of quazepam is common to other benzodiazepines.

Twelve healthy male volunteers received single oral 15 mg doses in [redacted] (used in clinical efficacy trials), tablet (intended for marketing), and suspension form in a crossover study design. A cross-over ANOVA extracting effects due to treatment, subject, and phase was performed on the data. There were no significant differences among the three formulations except for the first two hours following drug administration; during that time, the mean plasma levels were higher for the suspension and lowest for the capsule as expected. There were no significant differences among the three formulations with respect to AUC or between quazepam and 2-oxoquazepam with respect to Cmax indicating bioequivalence.

Twelve healthy male volunteers received single oral 15.0 mg, mg doses in tablet form in a crossover design study. The AUC/dose relationships were subjected to regression analyses which revealed an excellent linear relationship between mean AUC and dose for all three compounds. Dose proportionality was established for quazepam and its two major active metabolites.

Following single-dose oral administration of a 15 mg quazepam tablet to geriatric subjects (65-77 years of age), the drug is rapidly absorbed and is extensively distributed and/or metabolized. The pharmacokinetic parameters of quazepam and 2-oxoquazepam in geriatrics were comparable to those observed in young adult subjects, but the elimination half-life of N-desalkylflurazepam was about twice the corresponding $t_{1/2beta}$ in young adults.

Twelve healthy male volunteers recived single oral doses of 15 mg quazepam tablet once every 24 hours for 14 days. Steady-state levels of quazepam and 2-oxoquazepam were reached by the seventh dose and were not appreciably higher than those observed following the first dose. The steady-state of N-desalkylflurazepam was reached by the thirteenth dose (as predicted from previously attained single dose data). The steady state levels of N-desalkylflurazepam were about five fold higher than those observed after the first dose and were not unexpected since the half-life of this metabolite is three times greater than the dosing interval. This is similar to what has been observed for the N-desalkyl metabolites of diazepam, flurazepam, and medazepam.

In a cross-over, open-label fashion, twelve healthy male volunteers received one 15 mg tablet of quazepam either at night just prior to sleep or in the morning following a night's sleep. Results indicated that the pharmacokinetics of quazepam and its major active plasma metabolites are not appreciably altered by these two administration times. Administration of quazepam before sleep, however, yielded somewhat higher drug bioavailability than the same dose given in the morning. The Cmax and AUC for quazepam and 2-oxoquazepam and the AUC for N-desalkylflurazepam were consistently higher following the nighttime dose.

Four healthy, nonpregnant lactating female volunteers received a single oral 15 mg quazepam tablet. There was excretion of quazepam and its two major active metabolites into breast milk although through 48 hours following this single administration, excretion in breast milk was only 0.11% of the administered quazepam dose.

Overall Conclusion:

This application for Quazepam (15 mg Tablet) is approvable by the Division of Biopharmaceutics. However, the sponsor should agree to conduct additional dissolution testing to search for a more acceptable dissolution media as outlined in Comment #4 of the review.

Jerome P. Skelly, Ph.D.
Acting Director, Division of Biopharmaceutics

FT INITIALED BY ED PURICH Edward D. Purich

Prepared by: Karen B. Oseekey

kk:5/5/83:([redacted]

cc: HFN-120 (Leber), HFN-520 (Skelly), HFN-525 (Oseekey), Drug, Chron, Review.

Quazepam
15 mg and Tablet
NDA 18-708
Reviewer: K.B. Oseekey
Wang [redacted]

Schering Corporation
Bloomfield, N.J.
Submission date
April 2, 1982

Review of 8 Bioavailability Studies

Background:

Quazepam, was developed as a hypnotic compound in the benzodiazepine family and has been shown to be an effective sedative hypnotic drug in man. Quazepam is indicated for the treatment of all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, early morning awakenings, insomnia in geriatric patients, and in those patients requiring a rapid acting hypnotic for insomnia associated with situational stress or crisis, such as that experienced prior to surgery.

Analytical Methodology:

The method of analysis for quazepam and Sch 15725 (2-oxoquazepam) involved plasma extraction with [redacted] followed by chromatography on [redacted] at [redacted] and electron capture detection. The compounds were quantitated from plasma using [redacted] as the internal standard. The method was shown to be linear over the concentration range of [redacted] to [redacted] ng/ml, reproducible (within 6.5%CV), and sensitive by assaying pure standards of the compounds in plasma. The specificity of the method was established by comparing retention times of quazepam, Sch 15725, and [redacted] to those of other quazepam metabolites and flurazepam and finding no interferences. The lower limit of quantitation was [redacted] ng/ml plasma for both compounds. This method of analysis was found to be acceptable.

The method of analysis for Sch 17514 (N-desalkylflurazepam) involved plasma extraction with [redacted] following a cyclohexane washing of the plasma. The toluene extract was chromatographed on [redacted] at [redacted] with electron capture detection. Sch 17514 was quantitated from plasma using [redacted] as the internal standard. The method was shown to be linear over the concentration range of [redacted] to [redacted] ng/ml, reproducible (within 6.5 % CV) and sensitive by assaying pure standards of the compound in plasma. The specificity of the method was established by comparing retention times of Sch 17514 and Sch [redacted] to those of other quazepam metabolites and flurazepam and finding no interferences. The lower limit of quantitation for Sch 17514 was [redacted] ng/ml plasma. This method of analysis was found to be acceptable.

Study 1 ([redacted]) Previously reported as document no. P-4624, (May 1979).

Pilot Study: Feasibility and Sensitivity of an Assay Method and Preliminary Pharmacokinetics for Quazepam

Investigator/Institution:

Miguel Zenny, M.D.

[redacted]

Objectives:

To test feasibility of the GLC method developed for the assay of quazepam and its major active plasma metabolite (2 - oxoquazepam).

To serve as a preliminary evaluation for the pharmacokinetics of these compounds.

Study Design:

Six adult male volunteers, 21-29 years of age, completed this study. Good health was ascertained by medical history, physical examination, EKG and routine laboratory tests (hematology, blood chemistries and urinalysis).

Each subject received one 15 mg quazepam capsule (FMR No 776480-02, Batch No. 9383-104). Blood samples were collected prior to and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 48, 72, 96, and 120 hours after drug administration. Urine was collected just prior to drug administration (0 hour) and then in block samples at 0 to 4, 4 to 8, 8 to 12, 12 to 24, 24 to 48, 48 to 72, 72 to 96 and 96 to 120 hours after dosing. These samples were analysed by the Drug Metabolism and Pharmacokinetics Department, Pharmaceutical Research Division, Schering Corporation via a gas - liquid chromatographic method.

Results/Conclusions:

The GLC method was found suitable for measuring quazepam and 2 - oxoquazepam plasma levels for at least 48 hours following drug administration.

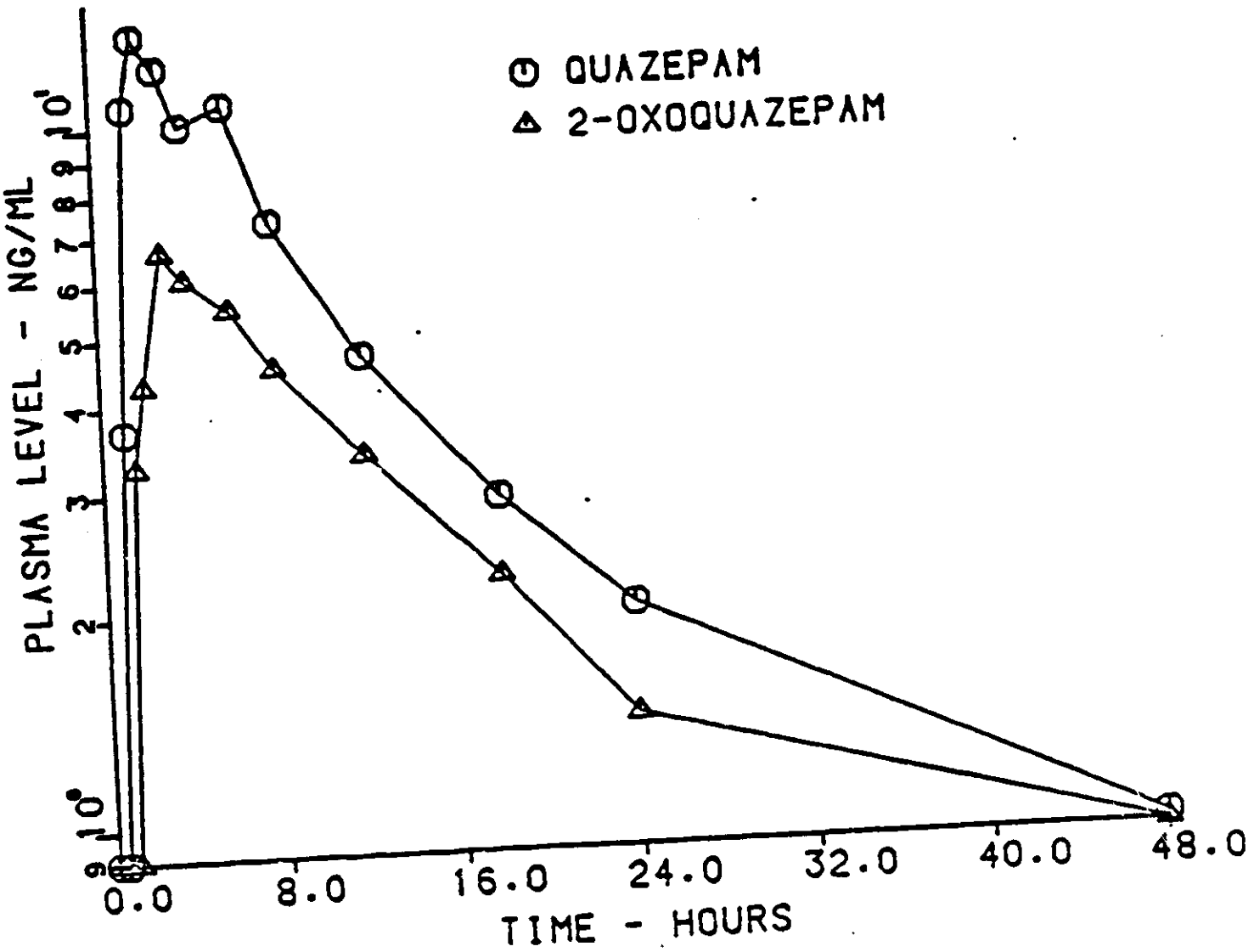
Summary data table I/figure I follow.

Pharmacokinetic analysis revealed the drug to be rapidly and well absorbed with peak plasma levels reached at approximately three hours; 2-oxoquazepam was rapidly formed with peak plasma levels occurring at about four hours. Both compounds declined in comparable biphasic patterns, with elimination half-lives of approximately 40 hours.

The concentrations of quazepam in the urine were below the detectability limits of the assay at all time points; those of 2-oxoquazepam, although low, were detectable for the first 24 hours following drug administration. See Table II.

STUDY NO. [redacted]

Figure 1. Mean (n=6) plasma concentration-time curves of quazepam and 2-oxoquazepam following oral administration of a single 15 mg quazepam capsule.



STUDY NO. [redacted] Page [redacted]

TABLE 7

PHARMACOKINETIC PARAMETERS OF QUAZEPAM AND 2-OXOQUAZEPAM FOLLOWING ORAL ADMINISTRATION OF A 15 MG QUAZEPAM CAPSULE

		Subject No.							
	Parameter*	1	2	3	4	5	6	Mean	SD
Quazepam	$t_{\frac{1}{2}}\alpha$							4.23	1.17
	$t_{\frac{1}{2}}\beta$							37.16	10.65
	AUC(∞)							226.24	84.87
	Cmax							17.50	7.69
	Tmax							2.80	1.70
2-oxoquazepam	$t_{\frac{1}{2}}\alpha$							2.95	1.38
	$t_{\frac{1}{2}}\beta$							29.90	8.51
	AUC(∞)							150.55	56.50
	Cmax							7.29	2.51
	Tmax							3.90	2.50

* $t_{\frac{1}{2}}\alpha$ and $t_{\frac{1}{2}}\beta$ are disposition half-lives (hours) in the distribution and elimination phases, respectively; AUC(∞) is the total area under the plasma drug concentration-time curve (hr x ng/ml); Tmax is the time (hour) at which maximum plasma concentration (Cmax) (ng/ml) was reached.

Data recorded in Schering Notebook No. [redacted] pages [redacted]

STUDY NO. [redacted]

Page [redacted]

TABLE 6

URINE CONCENTRATIONS OF 2-OXOQUAZEPAM (NG/ML) FOLLOWING ORAL ADMINISTRATION OF A SINGLE 15 MG QUAZEPAM CAPSULE

Subject No.	Block Sampling Times (hr postdose)				
	0-4	4-8	8-12	12-24	24-48
1					
2					
3					
4					
5					
6					

* ND=not detectable or below the confidence limit of assay.

Data recorded in Schering Notebook No. [redacted] page [redacted]

Study 2 [redacted] Previously reported as document nos., P-4635 (July 1979) and P-4645 (October 1979).

Acsorption, Distribution, Metabolism, and Excretion Study in Normal Male Volunteers.

Objective:

To investigate the absorption, distribution, metabolism and excretion of quazepam following a single oral dose of ^{14}C - quazepam.

Investigator/Institution:

Miguel A. Zinny, M.D.
[redacted]

Study Design:

Six adult male volunteers, 20-32 years of age, completed this study. Good health was ascertained by medical history, physical examination, EKG and routine laboratory tests (hematology, blood chemistries, and urinalysis).

Each subject received a single oral 25 mg dose of ^{14}C - quazepam in solution form. Blood samples were collected prior to and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 48, 72, 96 and 120 hours after drug administration. Urine was collected just prior to drug administration and then in block samples at 0-12, 12-24, 24-48, 48-72, 72-96 and 96-120 hours after dosing. Feces was also collected prior to drug adminstration and then up to 120 hours after dosing.

All biological specimens were analyzed for total radioactivity by liquid scintillation spectrometry. Plasma samples were analyzed for quazepam and two pharmacocologically active metabolites, 2-oxoquazepam and N-desalkylflurzepam by GLC methods. Plasma samples were analyzed for quazepam and two pharmacologically active metabolites, 2-oxoquazepam and N-desalkylflurzepam by GLC methods. Plasma and urine samples were analyzed by TLC for the metabolic profile.

Results:

Plasma levels were subjected to pharmacokinetic analysis using 2-compartment open model with first-order absorption/formation kinetics.

Total Radioactivity

k_a = 2.2 hr^{-1}
C_{max} = 324.6 ng-equiv/ml
T_{max} = 1.8 hours
$t_{1/2}$ alpha = 1.9 hours
$t_{1/2}$ beta = 75.6 hours
AUC_{0-120} = 11402.3 hr - ng/ml

The drug was extensively distributed and/or metabolized in the body as indicated by the large V_D value (2.22 L/kg). The K_{12} (0.18 hr^{-1}) value is comparable to that of K_{el} (0.22 hr^{-1}) but larger than that of K_{el} (0.035 hr^{-1}). This indicates that the disposition (elimination) of quazepam (Sch 16134) in man is rate-limiting by clearance of the drug from the tissue compartment.

The AUC (120 hr) was 714.55 ng-hr/ml or 94% of $AUC_{infinity}$. This suggests that the elimination of Sch 161341 is essentially completed by 120 hr.

Quazepam

k_a = 3.8 ± 3.3 hr^{-1}
C_{max} = 148.0 ± 64.9 ng/ml
T_{max} = 1.5 ± 0.4 hours
$t_{1/2}$ alpha = 1.7 ± 0.3
$t_{1/2}$ beta = 39.3 ± 10.7 hours
AUC_{0-120} = 714.6 ± 206.3 hr.-ng/ml

Following drug administration, the formation of 2-oxoquazepam (Sch 15725) is rapid, as indicated by the large k_m (2.19 hr^{-1}) and the short T_{max} (1.6 hr) values. Its elimination is essentially completed by 120 hr, since AUC (120 hr) is 93% $AUC_{infinity}$.

2 - Oxoquazepam

k_m = 2.2 ± 1.6 hr^{-1}
C_{max} = 45.6 ± 15.6 ng/ml
T_{max} = 1.6 ± 0.5 hours
$t_{1/2}$ alpha = 2.9 ± 1.2 hours
$t_{1/2}$ beta = 40.2 ± 10.2 hours
AUC_{0-120} = 438.3 ± 106.5 hr - ng/ml

The data pertaining to N-desalkylflurazepam were best fitted by a triexponential equation. The ratio of formation of this metabolite is fairly slow as indicated by its small k_m (0.80 hr^{-1}) and longer T_{max} (14.0 hr) values. The AUC (120 hr) is 68% of AUC (infinity) which suggests that about 30% of this metabolite remains to be excreted from the body after 120 hr.

N - desalkylflurazepam

k_m = 0.8 ± 0.3 hr^{-1}.
C_{max} = 40.9 ± 13.7 ng/ml
T_{max} = 14 ± 7.9 hours
$t_{1/2}$ alpha = 27.8 ± 8.0 hours
$t_{1/2}$ beta = 69.5 ± 19.6 hours
AUC_{0-120} = 3323.5 ± 116.8 hr-ng/ml

Conclusion/Discussion:

Following oral administration of ^{14}C - quazepam in solution form, the drug is rapidly and extensively absorbed, distributed, metabolized and slowly excreted in the urine and feces.

It was noted that although elimination half-lives indicated no differences from the administration of quazepam in suspension, tablet, or capsule vs ^{14}C labeled quazepam in solution, the magnitude of the C_{max}'s and AUC's were dramatically higher when solution was administered. This finding was discussed during a recent telephone conversation with Dr. Richard Gural, Project Monitor and Director of Clinical Drug Metabolism. It seems that this unique solution contains sufficient alcohol and propylene glycol to solubilize quazepam and allow for this substantial increase in rate and extent of aborption. (T_{max} was 1.5 hours rather than approximately 2.5 hours as observed for the other oral forms although inter-subject variability was large).

The metabolic pathway following administration of quazepam (Figure II follows) is common to other benzodiazepines. (Data - Tables III-V).

Study 3 [redacted]. Previously reported as document no. P-4704, (August 1980).

Comparative Bioavailability of Quazepam in Normal Male Volunteers: Three-Way Crossover Design.

Objective:

To compare the bioavailability and bioequivalency of quazepam following single oral 15 mg doses in capsule (used in clinical efficacy trials), tablet (intended for marketing), and suspension form.

Investigator/Institution:

John J. Hanigan, M.D.
[redacted]

Study Design:

Twelve adult males, 20-39 years of age, completed this study. Good health was ascertained by medical history, physical examination, EKG and routine clinical laboratories (hematology, blood chemistries, and urinalysis).

In a three-way randomized cross-over fashion, each subject received a single oral 15 mg dose of quazepam either as a capsule (FMR No. [redacted] Batch No. 10523-132), tablet (FMR No. [redacted] Batch No. 10392-127), or suspension (FMR No. [redacted] Batch No. 11194-42)(methylcellulose base). A four week washout priod separated the phases. Blood samples were collected prior to and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 48, 72, 96, 120, 144, 240 and 336 hours (14 days) after drug administration.

Plasma samples were assayed by a validated GLC method to determine levels of quazepam and two major active metabolites (2-oxoquazepam) and N - desalkylflurazepam). These plasma levels were used to determine the

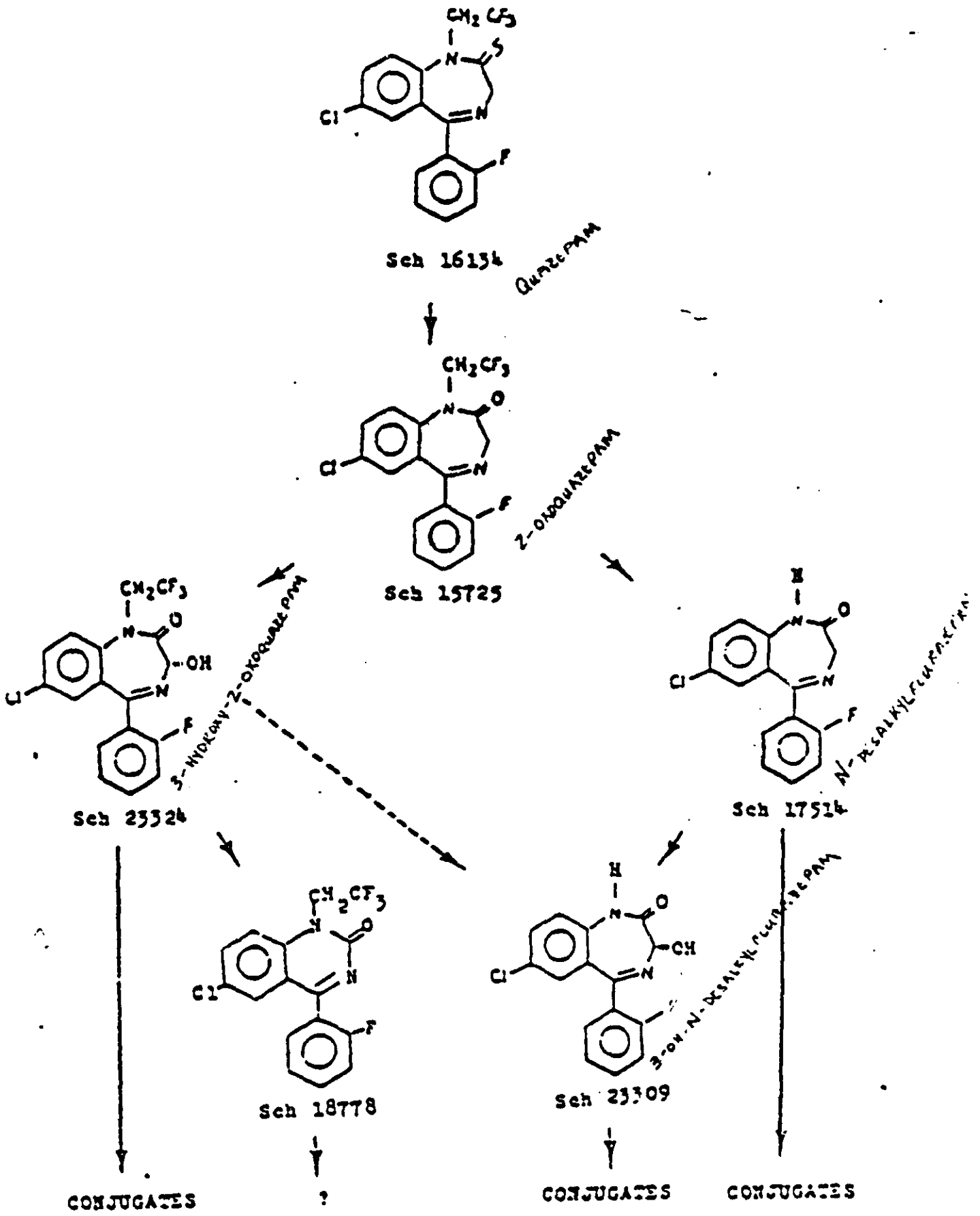


Fig. 15: Proposed metabolic scheme of quazepam

major bioavailability parameters (C_{max}, T_{max} and AUC) of the compounds, and plasma levels of N-desalkylflurazepam were used to determine only AUC for that compound.

Data Analysis:

The power to detect a 20% difference (alpha = 0.05) in bioavailability among the formulations was low (less than or equal to 0.35) for all three compounds, mainly due to large inter-subject variations in plasma levels at many time points; this is often seen with compounds which undergo rapid, extensive, and complex metabolism.

All data were subjected to a cross-over ANOVA extracting effects due to treatment, subject, and phase. These data are found in the following tables (MI-VIII). This anlysis showed that there were no significant differences (p = 0.05) among the three formulations, except for the first 2 hours following drug administrations. During that time, the mean plasma levels were higher for the suspension and lowest for the capsule as expected since absorption is faster from supsension formulations than fr. solid dosage forms. There were no significant differences among the three formulations with respect to AUC or between quazepam and 2-oxoquazepam with respect to C_{max}.

Conclusion:

The results of this study demonstrate that following single oral doses, the three formulations (capsule, tablet, and suspension), each containing 15 mg of quazepam, are bioequivalent.

Study 4 [redacted]

Dose Proportionality Study of Quazepam in Normal Male Volunteers: Three Way Crossover Design.

Objective:

To evaluate the dose proportionality of quazepam administered in tablet dosage form at single doses of 7.5, 15, and 30 mg.

Investigator/Institution:

Jules Kann, M.D., Ph.D.
[redacted]

Study Design:

Twelve adult male volunteers, 19-35 years of age, completed this study. Good health was ascertained by medical history, physical examination, EKG, and routine laboratory tests (hematology, blood chemistries, and urinalysis).

TABLE 3

Pharmacokinetic Parameters of Sch 16134 in Normal Male Volunteers Following a Single Oral Administration of 25 mg ^{14}C-Sch 16134 in Solution

	Subject No.						
Parameter*	1	2	3	4	5	6	Mean ± SD
K_a							3.79 ± 3.28
K_{12}							0.18 ± 0.05
K_{el}							0.22 ± 0.03
K_{21}							0.035± 0.009
V_p							2.22 ± 0.71
t_{lag}							0.40 ± 0.03
α							0.42 ± 0.07
β							0.019± 0.005
$t_{\frac{1}{2}}(K_a)$							0.37 ± 0.30
$t_{\frac{1}{2}}(\alpha)$							1.70 ± 0.28
$t_{\frac{1}{2}}(\beta)$							39.26 ± 10.70
TBC							590.83 ± 176.58
AUC(120 hr)							714.55 ± 206.29
AUC(∞)							759.58 ± 219.93
C_{max}							148.02 ± 64.94
T_{max}							1.50 ± 0.45

* Definitions and units of pharmacokinetic parameters are given in Table 1.

Data recorded in Schering Notebook No. [redacted] p. 14

TABLE 5

P-4645

TABLE 5

Pharmacokinetic Parameters of Sch 15725 in Normal Male Volunteers Following a Single Oral Administration of 25 mg ^{14}C-Sch 16134 in Solution

Parameter*	Subject No. 1	2	3	4	55	6	Mean ± SD
A_1							5.07 ± 1.83
A_2							66.41 ± 28.78
A_3							186.97 ± 150.08
K_m							2.19 ± 1.59
α							0.28 ± 0.11
β							0.018± 0.005
$t_{\frac{1}{2}}(K_m)$							0.49 ± 0.33
$t_{\frac{1}{2}}(\alpha)$							2.87 ± 1.24
$t_{\frac{1}{2}}(\beta)$							40.16 ± 10.16
AUC(120 hr)							438.32 ± 106.51
AUC(∞)							472.66 ± 104.74
C_{max}							45.60 ± 15.63
T_{max}							1.58 ± 0.49

* Definitions and units of pharmacokinetic parameters are given in Table 1.

Data recorded in Schering Notebook No. [redacted]

TABLE 7

Pharmacokinetic Parameters of Sch 17514 in Normal Male Volunteers Following a Single Oral Administration of 25 mg ^{14}C-Sch 16134 in Solution

Parameter*	Subject No. 1	2	3	4	5	6	Mean ± SD
A_1							70.03 ± 38.76
A_2							35.01 ± 32.33
A_3							45.28 ± 14.06
K_a							0.80 ± 0.30
α							0.027± 0.009
β							0.011± 0.002
$t_{\frac{1}{2}}(K_a)$							0.91 ± 0.29
$t_{\frac{1}{2}}(\alpha)$							27.80 ± 8.00
$t_{\frac{1}{2}}(\beta)$							69.46 ± 19.59
AUC(120 hr)							3323.45 ±1116.79
AUC(∞)							4907.99 ±1263.29
C_{max}							40.94 ± 13.74
T_{max}							14.00 ± 7.90

* Definitions and units of pharmacokinetic parameters are given in Table 1.

Data recorded in Schering Notebook No. [redacted]

STUDY NO. [redacted]

TABLE 8

MEAN PLASMA LEVELS, BIOAVAILABILITY/BIOEQUIVALENCY PARAMETERS, AND STATISTICAL COMPARISONS OF QUAZEPAM FOLLOWING ADMINISTRATION OF A SINGLE 15 MG DOSE OF QUAZEPAM IN CAPSULE, TABLET, AND SUSPENSION FORMS

Mean (% CV)

Parameter	Treatments			Statistical Comparison*		
Plasma Levels (ng/ml) Time (hr)	A	B	C	A:B	B:C	A:C
0	0.0	0.0	0.0	NS	NS	NS
0.25	0.0	0.0	1.0 (91)	NS	SIG	SIG
0.5	0.2 (149)	1.9 (119)	7.2 (68)	NS	SIG	SIG
0.75	1.2 (77)	8.9 (119)	14.3 (72)	SIG	NS	SIG
1	2.5 (54)	12.0 (111)	16.4 (66)	SIG	NS	SIG
1.5	6.9 (67)	14.4 (64)	16.1 (52)	SIG	NS	SIG
2	9.7 (57)	15.8 (61)	17.7 (64)	SIG	NS	SIG
3	13.7 (57)	17.5 (45)	14.2 (49)	NS	NS	NS
4	11.5 (45)	13.2 (34)	11.2 (41)	NS	NS	NS
6	9.5 (49)	8.7 (31)	6.5 (35)	NS	NS	SIG
8	6.9 (40)	5.8 (36)	4.7 (44)	NS	NS	SIG
12	3.6 (38)	3.5 (28)	3.1 (58)	NS	NS	NS
18	2.5 (53)	2.3 (35)	2.1 (47)	NS	NS	NS
24	1.8 (55)	1.7 (35)	1.5 (37)	NS	NS	NS
48	0.9 (62)	0.8 (44)	0.7 (66)	NS	NS	NS
72	0.5 (119)	0.4 (91)	0.3 (112)	NS	NS	NS
96	0.2 (193)	0.2 (153)	0.2 (183)	NS	NS	NS
120	0.1 (237)	0.1 (186)	0.1 (346)	NS	NS	NS
144	0.1 (234)	0.1 (346)	0.0	NS	NS	NS
240	0.0	0.0	0.0	NS	NS	NS
336	0.0	0.0	0.0	NS	NS	NS
Cmax (ng/ml)	15.6 (45)	21.9 (47)	20.9 (61)	NS	NS	NS
Tmax (hr)	3.3 (44)	2.5 (57)	1.6 (46)	NS	NS	SIG
AUC (hr x ng/ml)	191.3 (48)	195.3 (37)	171.1 (47)	NS	NS	NS

* Pairwise comparisons of treatments, where NS=nonsignificant difference at $p \geq .05$ and SIG=significant difference at $p < .05$.

Treatments: A=capsule, B=tablet, and C=suspension.

[redacted]

STUDY NO. [redacted]

TABLE 9

MEAN PLASMA LEVELS, BIOAVAILABILITY/BIOEQUIVALENCY PARAMETERS, AND STATISTICAL COMPARISONS OF 2-OXOQUAZEPAM FOLLOWING ADMINISTRATION OF A SINGLE 15 MG DOSE OF QUAZEPAM IN CAPSULE, TABLET, AND SUSPENSION FORMS

Mean (% CV)

Parameter	Treatments			Statistical Comparison*		
Plasma Levels (ng/ml) Time (hr)	A	B	C	A:B	B:C	A:C
0	0.0	0.0	0.0	NS	NS	NS
0.25	0.0	0.0	0.0	NS	NS	NS
0.5	0.0	0.4 (150)	3.2 (61)	NS	SIG	SIG
0.75	0.5 (106)	3.4 (130)	6.7 (56)	SIG	SIG	SIG
1	1.6 (89)	4.9 (110)	7.9 (53)	SIG	NS	SIG
1.5	3.5 (57)	6.6 (77)	8.2 (35)	SIG	NS	SIG
2	5.0 (55)	7.8 (56)	8.4 (48)	SIG	NS	SIG
3	7.4 (63)	10.2 (45)	8.2 (37)	SIG	NS	NS
4	7.1 (52)	8.7 (36)	7.2 (33)	NS	NS	NS
6	6.0 (46)	6.0 (31)	4.4 (32)	NS	NS	NS
8	4.6 (41)	4.6 (27)	3.7 (34)	NS	NS	NS
12	2.7 (33)	3.0 (21)	2.5 (35)	NS	NS	NS
18	2.0 (28)	2.0 (15)	1.7 (36)	NS	NS	NS
24	1.5 (39)	1.6 (19)	1.3 (34)	NS	NS	NS
48	0.6 (55)	0.8 (39)	0.5 (88)	NS	NS	NS
72	0.1 (190)	0.1 (185)	0.2 (167)	NS	NS	NS
96	0.1 (346)	0.1 (235)	0.2 (251)	NS	NS	NS
120	0.0	0.1 (234)	0.2 (256)	NS	NS	NS
144	0.0	0.0	0.0	NS	NS	NS
240	0.0	0.0	0.0	NS	NS	NS
336	0.0	0.0	0.0	NS	NS	NS
Cmax (ng/ml)	8.5 (52)	11.4 (43)	10.3 (37)	NS	NS	NS
Tmax (hr)	4.0 (38)	2.6 (31)	1.8 (56)	SIG	NS	SIG
AUC (hr x ng/ml)	118.4 (31)	138.3 (27)	122.1 (49)	NS	NS	NS

* Pairwise comparisons of treatments, where NS=nonsignificant difference at $p \geq .05$ and SIG=significant difference at $p < .05$.

Treatments: A=capsule, B=tablet, and C=suspension.

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TABLE 10

MEAN PLASMA LEVELS, AUC, AND STATISTICAL COMPARISONS OF N-DESALKYLFLURAZEPAM FOLLOWING ADMINISTRATION OF A SINGLE 15 MG DOSE OF QUAZEPAM IN CAPSULE, TABLET, AND SUSPENSION FORMS

Mean (% CV)

Parameter	Treatments			Statistical Comparison*		
Plasma Levels (ng/ml) Time (hr)	A	B	C	A:B	B:C	A:C
0	0.0	0.0	0.0	NS	NS	NS
0.25	0.0	0.1 (346)	0.3 (346)	NS	NS	NS
0.5	0.2 (346)	0.5 (181)	2.1 (106)	NS	SIG	SIG
0.75	1.2 (173)	2.1 (146)	5.5 (45)	NS	SIG	SIG
1	2.7 (165)	4.4 (116)	7.3 (37)	NS	NS	SIG
1.5	4.8 (137)	6.7 (81)	10.3 (50)	NS	NS	SIG
2	7.9 (131)	10.1 (84)	13.5 (46)	NS	NS	NS
3	13.1 (118)	13.8 (62)	15.6 (44)	NS	NS	NS
4	15.8 (113)	16.0 (61)	17.1 (46)	NS	NS	NS
6	19.1 (93)	17.7 (54)	18.5 (48)	NS	NS	NS
8	19.1 (76)	17.5 (41)	17.8 (42)	NS	NS	NS
12	19.0 (67)	17.3 (37)	18.5 (41)	NS	NS	NS
18	16.6 (57)	15.6 (37)	15.7 (35)	NS	NS	NS
24	15.2 (50)	16.3 (35)	16.3 (34)	NS	NS	NS
48	13.5 (32)	14.4 (28)	14.2 (29)	NS	NS	NS
72	10.8 (33)	11.9 (34)	12.8 (45)	NS	NS	NS
96	8.5 (36)	9.5 (27)	9.0 (27)	NS	NS	NS
120	6.8 (33)	7.7 (36)	7.1 (31)	NS	NS	NS
144	5.2 (44)	6.0 (37)	6.0 (36)	NS	NS	NS
240	2.4 (101)	2.3 (102)	2.9 (53)	NS	NS	NS
336	1.3 (168)	1.3 (118)	1.3 (130)	NS	NS	NS
AUC (hr x ng/ml)	2121.4 (29)	2246.0 (29)	2321.2 (25)	NS	NS	NS

* Pairwise comparisons of treatments, where NS=nonsignificant difference at $p \geq .05$ and SIG=significant difference at $p < .05$.

Treatments: A=capsule, B=tablet, and C=suspension.

In a three-way crossover design, each subject received a single oral dose of quazepam in tablet form at doses of
15 (FMR No. [redacted] Batch No. 11194-75), and
following a 10 hour fast and using a 28 day washout between treatment phases. Blood samples were collected prior to and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 48, 72, 96, 144, 192, and 240 hours after drug administration. Plasma samples were assayed by GC for levels of quazepam and its major metabolites, 2-oxoquazepam and N-desalkylflurazepam.

Results:

Plasma levels of quazepam and 2-oxoquazepam were used to determine the major bioavailability parameters (C_{max}, T_{max}, and AUC) for both compounds; plasma levels of N-desalkylflurazepam were used to determine only AUC for that compound since there is a plateauing of the N-desalkylflurazepam plasma levels from approximately 6 to 48 hours. These data are summarized in the following tables (IX-XI). The AUC/dose relationships were then subjected to regression analysis to evaluate dose proportionality between the three treatments. Regression analyses revealed excellent linear relationships between mean AUC and dose for all three compounds (r greater than 0.99).

Conclusion:

From the results of this study, it can be concluded that the 15, and mg tablets of quazepam, when administered as single doses, are dose proportional since dose proportionality was established for quazepam and its two major active plasma metabolites.

Study 5 [redacted]

Pharmacokinetics of Quazepam in Healthy Geriatric Volunteers

Objectives:

To determine the pharmacokinetics of quazepam and its major active plasma metabolites (2-oxoquazepam and N-desalkylflurazepam) in healthy geriatric subjects

To determine if the pharmacokinetics differ from those previously obtained in young adult volunteers.

Investigator/Institution:

Miguel A. Zinny, M.D.
[redacted]

Study Design:

Twelve geriatric volunteers (six males and six females), 65-77 years of age, completed this study. Good health was ascertained through medical

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TABLE 6

MEAN PLASMA CONCENTRATIONS AND BIOAVAILABILITY PARAMETERS OF QUAZEPAM FOLLOWING SINGLE-DOSE ADMINISTRATIONS OF [redacted] 15, AND [redacted] MG TABLETS

Mean (± CV)

Parameter	Treatments
Plasma Levels (ng/ml)	
Time (hr)	15 mg
0	0.0
0.5	1.0* (150)
1	7.2 (105)
1.5	11.9 (87)
2	13.4 (69)
3	17.9 (48)
4	15.2 (46)
6	10.1 (34)
8	7.4 (31)
12	5.0 (34)
16	3.7 (39)
24	2.6 (51)
48	1.2 (55)
72	0.9* (56)
96	0.6* (73)
144	0.3* (112)
192	0.0
240	0.0
Cmax (ng/ml)	19.3 (49)
Tmax (hr)	2.8 (28)
AUC (hr x ng/ml)	271.7 (38)

* Data used in the calculation of this mean value contained values below the assay sensitivity limit of 0.75 ng/ml.

TABLE I

STUDY NO. [redacted] Page [redacted]

TABLE 7

MEAN PLASMA CONCENTRATIONS AND BIOAVAILABILITY PARAMETERS OF 2-OXOQUAZEPAM FOLLOWING SINGLE-DOSE ADMINISTRATIONS OF [redacted] 15, AND [redacted] MG QUAZEPAM TABLETS

Mean (% CV)

Parameter Plasma Levels (ng/ml) Time (hr)	Treatments 15 mg
0	0.0
0.5	0.4* (88)
1	2.7* (91)
1.5	4.8* (61)
2	5.3 (52)
3	8.2 (35)
4	7.4 (37)
6	5.5 (27)
8	4.4 (21)
12	3.2 (20)
16	2.4 (20)
24	1.8 (31)
48	0.9* (27)
72	0.7* (50)
96	0.5* (84)
144	0.2* (144)
192	0.0
240	0.0
Cmax (ng/ml)	8.4 (33)
Tmax (hr)	3.0 (23)
AUC (hr x ng/ml)	169.4 (27)

* Data used in the calculation of this mean value contained values below the assay sensitivity limit of 0.75 ng/ml.

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TABLE 8

MEAN PLASMA CONCENTRATIONS AND AUC OF N-DESALKYLFLURAZEPAM FOLLOWING SINGLE-DOSE ADMINISTRATIONS OF [redacted] 15, AND [redacted] MG QUAZEPAM TABLETS

Mean (% CV)

Parameter Plasma Levels (ng/ml) Time (hr)	Treatments 15 mg
0	0.4* (129)
0.5	0.9* (94)
1	3.2 (96)
1.5	5.9 (86)
2	6.7 (81)
3	11.2 (46)
4	12.5 (44)
6	14.6 (47)
8	15.5 (48)
12	15.8 (39)
16	16.8 (44)
24	15.0 (39)
48	14.9 (42)
72	13.9 (35)
96	11.4 (35)
144	8.1 (30)
192	5.5 (28)
240	4.3 (32)
AUC (hr x ng/ml)	2377.0 (31)

* Data used in the calculation of this mean value contained values below the assay sensitivity limit of 1.5 ng/ml.

history, physical examination; EKG, and routine laboratory tests (hematology, blood chemistries, and urinalysis).

In an open - label fashion, each subject received a single oral 15 mg tablet (FMI No. [redacted] of quazepam. Blood samples were collected prior to and at 1, 2, 4, 8, 12, 16, 24, 48, 72, 120, 168, 240, 336, 408, 504, 576 and 672 hours (28 days) after drug administration.

Plasma samples were assayed by GC to determine levels of quazepam, 2-oxoquazepam, and N-desalkylflurazepam. Plasma levels of quazepam and 2-oxoquazepam were used to determine the major bioavailability parameters (C_{max}, T_{max}, and AUC) for both compounds; plasma levels of N-desalkylflurazepam were used to determine only AUC for that compound. All data were then subjected to pharmacokinetic analysis using a two-compartment open model with 1st order absorption/formation kinetics.

Results:

Following oral administration, the drug was rapidly absorbed (k_a = 1.1 hr^{-1}) with a Cmax of 29.3 ng/ml at 2.7 hours (T_{max}). The drug was extensively distributed and/or metabolized as indicated by a V_p of 6.4 liter/kg.

The disposition half-lives of quazepam in geriatrics ($t_{1/2alpha}$ = 3.5 hours, $t_{1/2beta}$ = 53.3 hours) were only slightly greater and total body clearance (595 ml/min) was comparable to values observed in young adult subjects.

The formation of 2-oxoquazepam was rapid (k_m = 1.1 hr. -1) with a C_{max} of 14.5 ng/ml at 3 hours (T_{max}). The disposition half-life kinetics $t_{1/2alpha}$ = 4.21 hours, $t_{1/2beta}$ = 43.08 hours were comparable to those of the parent drug.

The C_{max} of N-desalkylflurazepam (range [redacted] to [redacted] ng/ml) exhibited a plateau from four to 120 hours and the elimination half-life ($t_{1/2beta}$) was 189.7 hours, which was much longer than that of its precursor, 2 - oxoquazepam, and about twice that observed in young adults.

These results are summarized in the following table (XII).

Conclusion:

Following single-dose oral administration of a 15 mg quazepam tablet to geriatric subjects, the drug is rapidly absorbed and is extensively distributed and/or metabolized. Pharmacokinetics of the rapidly formed quazepam metabolite, 2-oxoquazepam, are comparable to the parent drug, but the elimination half-life of N-desalkylflurazepam was much longer than that of its precursor, 2-oxoquazepam.

The pharmacokinetic parameters of quazepam and 2 - oxoquazepam in geriatrics were comparable to those observed in young adult subjects but the $t_{1/2beta}$ of N-desalkylflurazepam was much longer than the corresponding elimination half-life in young adults.

TABLE 5

MEAN (N=10) PLASMA LEVELS, BIOAVAILABILITY PARAMETERS, AND PHARMACOKINETIC PARAMETERS OF QUAZEPAM AND ITS MAJOR ACTIVE PLASMA METABOLITES FOLLOWING SINGLE ORAL ADMINISTRATION OF A 15 MG QUAZEPAM TABLET IN HEALTHY GERIATRIC SUBJECTS

Parameter / Plasma Levels (ng/ml) / Time (hr)	Mean (% CV) Quazepam	2-oxoquazepam	N-desalkylflurazepam
0	0	0	0
1	19.0 (65)	8.1 (69)	4.1 (77)*
2	26.9 (34)	13.1 (43)	7.7 (56)
4	17.8 (39)	10.5 (42)	10.5 (47)
8	10.5 (47)	6.4 (24)	11.4 (39)
12	7.8 (52)	4.6 (29)	10.7 (33)
16	5.7 (45)	3.4 (22)	11.2 (26)
24	4.6 (66)	2.7 (39)	11.6 (23)
48	2.3 (53)	1.5 (54)*	13.1 (12)
72	1.5 (46)	0.8 (72)*	12.8 (22)
120	0.9 (87)*	0.4 (104)*	11.5 (21)
168	0.5 (116)*	0.2 (167)*	9.3 (34)
240	0.3 (175)*	0.1 (214)*	6.1 (46)
336	0.1 (300)*	0	5.5 (41)
408	0	0	4.0 (68)*
504	0	0	3.0 (77)*
576	0	0	2.1 (93)*
672	0	0	1.8 (106)*
Cmax (ng/ml)	29.3 (31)	14.5 (38)	—
Tmax (hr)	2.7 (74)	3.0 (65)	—
AUC (hr x ng/ml)	509.6 (50)	275.1 (41)	4075.0 (32)
$t_{\frac{1}{2}}ka$ (hr)	0.81 (60)	—	—
$t_{\frac{1}{2}}ka$ (hr)	—	0.83 (65)	0.60 (60)
$t_{\frac{1}{2}}\alpha$ (hr)	3.5 (102)	4.2 (122)	40.3 (114)
$t_{\frac{1}{2}}\beta$ (hr)	53.3 (74)	43.1 (65)	189.7 (53)
V_p (liter/kg)	6.4 (50)	—	—
TFC (ml/min)	594.7 (46)	—	—

* Individual data at these time points contained values below assay sensitivity limits.

Study 6 [redacted]

Steady-State Evaluation of Quazepam in Healthy Adult Male Volunteers.

Objective:

To investigate the steady state plasma levels and evaluate the steady-state pharmacokinetics of quazepam and its major active plasma metabolites, 2-oxoquazepam and N-desalkyflurazepam. (multiple dose).

Investigator/Institution:

Albert Cohen, M.D.
[redacted]

Study Design:

Twelve healthy adult male volunteers, 19-39 years of age, were empanelled, eleven of whom completed the study. Good health was ascertained through medical history, physical examination, EKG and routine laboratory tests (hematology, blood chemistries, and urinalysis).

Each subject received one (1) 15 mg, quazepam tablet (FMR No. [redacted] Batch No. 12071-97) once every 24 hours for 14 days. Blood samples were collected prior to and at 1, 2, 3, 4, 6, 10, 16, and 24 hours following drug administrations on days 1, 7, 8, 13, and 14. On days 4 and 11, blood samples were collected at 0, 4, 16, and 24 hours. Additional blood samples were collected at 36, 48, 72, 96, 120, 216, and 312 hours following day 14 of dosing.

Plasma samples were analyzed by GC to determine levels of quazepam and its major active metabolites . Plasma levels of quazepam ad 2-oxoquazepam were used to determine the bioavailability parameters C_{max}, T_{max}, and AUC for both compounds; plasma levels of N-desalkylflurazepam were used to determine only AUC for that compound. All data were subjected to pharmacokinetic analysis using a two-compartment open model with first - order absorption/formation kinetics for quazepam and 2-oxoquazepam.

Results:

Quazepam was rapidly absorbed following oral administration with a $t_{1/2}$ k_a of 1.1 hours. The disposition kinetics showed that there was a rapid initial distribution phase with a half-life of 1.9 hours ($t_{1/2alpha}$) followed by a slower elimination phase with a half-life of 40.8 hours ($t_{1/2beta}$). Steady-state of quazepam was reached by the seventh dose (as predicted from previously attained single dose data) and plasma levels were not appreciably higher than those observed following the first dose.

2-Oxoquazepam was formed rapidly from quazepam ($t_{1/2Km}$ = 1.2 hours), and the disposition kinetics ($t_{1/2\ alpha}$ = 2.0 hours , $t_{1/2beta}$ = 43.1 hours) were comparable to those of the parent drug. Steady-state was also reached by the seventh dose and plasma levels were not appreciably higher than those observed following the first dose.

N-desalkylflurazepam was formed rapidly from 2-oxoquazepam and eliminated slowly with half-life ($t_{1/2beta}$) of 75 hours. Steady-state of N-desalkylflurazepam was reached by the 13th dose and plasma levels were appreciably greater than those observed after the first dose. Since the half-life of this metabolite is three times greater than the dosing interval, the higher steady-state levels were not unexpected.

Data from this study are summarized in the following tables (XIII-XVI).

Conclusions:

Following daily oral administration of a 15 mg quazepam tablet, steady-state levels of quazepam and 2-oxoquazepam are reached by the seventh dose and the steady-state of N-desalkylflurazepam is reached by the 13th dose. The steady-state levels of N-desalkylflurzepam were about fivefold higher than those observed after the first dose. This is similar to what has been observed for the N-desalkyl metabolites of diazepam, flurazepam, and medazepam.

Steady-state pharmacokinetics of these compounds can be accurately predicted from plasma levels attained from single-dose administration of quazepam.

Study 7 [redacted]

Effect of Sleep on the Disposition Characteristics of Quazepam.

Objective:

To determine the effect of sleep on the pharmacokinetics of quazepam.

Investigator/Institution:

Elwood Buchman, M.D.
[redacted]

Study Design:

Twelve adult male volunteers, 19-36 years of age, completed this study. Good health was ascertained through medical history, physical examination, EKG, and routine laboratory tests (hematology, blood chemistries, and urinalysis).

In a two-way cross-over, open-label fashion, each subject received one 15

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TABLE 6

MEAN (N=11) PLASMA CONCENTRATIONS, CMAX, TMAX, AND AUC_0^T OF QUAZEPAM FOLLOWING DAILY ADMINISTRATION OF A 15 MG QUAZEPAM TABLET FOR 14 DAYS

Mean (% CV)

Parameter / Plasma Levels (ng/ml) Time (hr)	Day 1	Day 4	Day 7	Day 8	Day 11	Day 13	Day 14
0.0	0.0	2.6 (74)	6.2 (62)	5.7 (45)	6.2 (49)	6.4 (61)	5.0 (63)
1.0	14.8 (55)		12.8 (60)	18.3 (63)		18.3 (63)	17.6 (66)
2.0	26.6 (83)		20.8 (36)	23.0 (44)		34.7 (49)	28.1 (61)
3.0	25.2 (63)		25.4 (33)	26.5 (42)		22.7 (56)	25.3 (56)
4.0	18.3 (56)	10.3 (38)	22.8 (36)	22.2 (47)	25.4 (36)	17.4 (62)	20.1 (59)
6.0	10.4 (42)		15.6 (40)	14.5 (40)		13.2 (61)	13.7 (63)
10.0	5.4 (49)		8.6 (53)	9.4 (52)		9.9 (62)	8.6 (68)
16.0	3.6 (32)	2.8 (38)	9.1 (51)	7.6 (49)	9.2 (48)	7.9 (64)	6.8 (65)
24.0	2.1 (38)	2.8 (52)	5.7 (45)	5.3 (48)	9.3 (52)	5.0 (63)	5.0 (63)
36.0							5.1 (73)
48.0							4.4 (67)
72.0							3.3 (74)
96.0							2.7 (65)
120.0							2.4 (73)
Cmax (ng/ml)	30.5 (72)		26.8 (28)	29.0 (47)		34.9 (48)	29.6 (57)
Tmax (hr)	2.5 (27)		2.7 (28)	2.6 (39)		1.9 (36)	2.2 (28)
AUC_0^T (hr x ng/ml)	185.4 (41)		273.0 (41)	268.9 (40)		269.3 (56)	255.3 (61)

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TABLE 6

MEAN (N=11) PLASMA CONCENTRATIONS, CMAX, TMAX, AND AUC_0^T OF QUAZEPAM FOLLOWING DAILY ADMINISTRATION OF A 15 MG QUAZEPAM TABLET FOR 14 DAYS

Mean (% CV)

Parameter / Plasma Levels (ng/ml) Time (hr)	Day 1	Day 4	Day 7	Day 8	Day 11	Day 13	Day 14
0.0	0.0	2.6 (74)	6.2 (62)	5.7 (45)	6.2 (49)	6.4 (61)	5.0 (63)
1.0	14.8 (55)		12.8 (60)	18.3 (63)		18.3 (63)	17.6 (66)
2.0	26.6 (83)		20.8 (36)	23.0 (44)		34.7 (49)	28.1 (61)
3.0	25.2 (63)		25.4 (33)	26.5 (42)		22.7 (56)	25.3 (56)
4.0	18.3 (56)	10.3 (38)	22.8 (36)	22.2 (47)	25.4 (36)	17.4 (62)	20.1 (59)
6.0	10.[illegible] (42)		15.6 (40)	14.5 (40)		13.2 (61)	13.7 (63)
10.0	5.4 (49)		8.6 (53)	9.4 (52)		9.9 (62)	8.6 (68)
16.0	3.6 (32)	2.8 (38)	9.1 (51)	7.6 (49)	9.2 (48)	7.9 (64)	6.8 (65)
24.0	2.1 (38)	2.8 (52)	5.7 (45)	5.3 (48)	9.3 (52)	5.0 (63)	5.0 (63)
36.0							5.1 (73)
48.0							4.4 (67)
72.0							3.3 (74)
96.0							2.7 (65)
120.0							2.4 (73)
Cmax (ng/ml)	30.5 (72)		26.8 (28)	29.0 (40)		[illegible].9 (48)	29.6 (57)
Tmax (hr)	2.5 (27)		2.7 (28)	2.6 (39)		1.9 (36)	2.2 (28)
AUC_0^T (hr x ng/ml)	185.4 (41)		273.0 (41)	268.9 (40)		269.3 (56)	255.3 (61)

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TABLE 7

MEAN (N=11) PLASMA CONCENTRATIONS, CMAX, TMAX, AND AUC_0^T OF 2-OXOQUAZEPAM FOLLOWING DAILY ADMINISTRATION OF A 15 MG QUAZEPAM TABLET FOR 14 DAYS

Mean (% CV)

Parameter / Plasma Levels (ng/ml) Time (hr)	Day 1	Day 4	Day 7	Day 8	Day 11	Day 13	Day 14
0.0	0.0	3.1 (39)	4.5 (38)	4.7 (28)	5.3 (27)	5.3 (40)	4.1 (48)
1.0	7.8 (69)		7.7 (48)	10.5 (41)		9.7 (59)	9.0 (56)
2.0	14.2 (60)		11.9 (38)	14.8 (33)		19.2 (49)	14.4 (49)
3.0	13.8 (50)		13.5 (21)	14.9 (26)		13.7 (53)	15.0 (54)
4.0	11.4 (32)	11.2 (22)	13.0 (22)	13.6 (27)	16.0 (27)	13.4 (57)	12.4 (49)
6.0	9.0 (27)		9.5 (32)	11.5 (39)		11.9 (52)	9.8 (57)
10.0	4.2 (69)		6.4 (28)	7.2 (24)		7.7 (45)	6.1 (47)
16.0	3.7 (90)	5.1 (26)	6.9 (29)	7.8 (97)	9.5 (56)	6.6 (49)	6.0 (47)
24.0	5.4 (157)	4.1 (32)	4.7 (28)	4.2 (29)	8.1 (28)	4.1 (48)	4.2 (50)
36.0							4.4 (48)
48.0							4.1 (42)
72.0							2.8 (60)
96.0							1.7 (42)
120.0							1.4 (53)
Cmax (ng/ml)	18.2 (42)		14.8 (20)	17.7 (35)		20.2 (47)	15.9 (50)
Tmax (hr)	4.5 (143)		2.9 (28)	3.9 (104)		1.8 (33)	2.5 (21)
AUC_0^T (hr x ng/ml)	148.1 (42)		182.1 (24)	208.1 (39)		183.0 (57)	177.7 (47)

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TABLE 8

MEAN (N=11) PLASMA CONCENTRATIONS AND AUC_0^T VALUES OF N-DESALKYLFLURAZEPAM FOLLOWING DAILY ADMINISTRATION OF A 15 MG QUAZEPAM TABLET FOR 14 DAYS

Mean (% CV)

Parameter Plasma Levels (ng/ml) Time (hr)	Day 1	Day 4	Day 7	Day 8	Day 11	Day 13	Day 14
0.0	0.0	59.0 (33)	86.8 (26)	67.9 (33)	71.1 (38)	127.7 (39)	86.3 (37)
1.0	8.2 (49)		99.1 (23)	72.4 (27)		73.0 (41)	97.1 (43)
2.0	16.5 (43)		74.2 (27)	76.4 (31)		160.9 (29)	113.6 (45)
3.0	20.1 (43)		81.4 (27)	90.5 (29)		151.9 (33)	88.3 (31)
4.0	23.2 (43)	75.0 (24)	85.0 (28)	96.3 (28)	98.5 (36)	129.7 (35)	107.0 (33)
6.0	23.6 (47)		75.4 (28)	90.1 (28)		125.5 (39)	108.0 (32)
10.0	21.2 (34)		73.1 (32)	70.7 (32)		69.2 (39)	86.0 (37)
16.0	20.5 (56)	77.4 (29)	70.2 (24)	79.0 (33)	93.3 (40)	72.8 (34)	93.0 (35)
24.0	19.9 (36)	72.9 (25)	67.9 (33)	71.8 (30)	88.1 (41)	86.3 (37)	75.9 (36)
36.0							111.3 (42)
48.0							98.2 (53)
72.0							69.9 (39)
96.0							64.1 (45)
120.0							58.2 (49)
AUC_0^T (hr x ng/ml)	479.5 (42)		1780.0 (27)	1921.7 (30)		2221.5 (33)	2211.2 (33)

Page [redacted]

Page

TABLE 9

MEAN (N=11) STEADY-STATE PHARMACOKINETIC PARAMETERS OF QUAZEPAM AND 2-OXOQUAZEPAM FOLLOWING DAILY ADMINISTRATION OF A 15 MG QUAZEPAM TABLET FOR 14 DAYS

Mean (% CV)

Parameter*	Quazepam	2-oxoquazepam
k_a	0.66 (33)	—
k	—	0.62 (26)
α	0.37 (19)	0.36 (25)
β	0.017 (12)	0.017 (13)
$t_{1/2}ka$	1.1 (27)	—
$t_{1/2}k$	—	1.2 (26)
$t_{1/2}\alpha$	1.9 (24)	2.0 (20)
$t_{1/2}\beta$	40.8 (14)	43.1 (16)

* Definitions and units are shown in Appendix B (Table 1).

mg tablet of quazepam (FMR No. [redacted] Batch No. 12071-97) either at night just prior to sleep or in the morning following a night's sleep with a one-month washout period separating each treatment phase. Blood samples were collected before and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 16, 24, 48, 72, 96, and 120 hours following drug administration. An indwelling catheter placed in a large arm vein was used as not to interfere with sleep during that treatment phase; this procedure was used for the collection of blood samples over the first 24-hour period postdosing.

Plasma samples were analyzed by a GLC method. Plasma levels of quazepam and 2 - oxoquazepam were used to determine C_{max}, T_{max}, and AUC for both compounds; plasma levels of N-desalkylflurazepam were used to determine only AUC for that compound.

The plasma quazepam concentrations (C_p) in each subject following a single oral administration of a 15 mg quazepam tablet in the morning or just prior to sleep were analyzed by a two-compartment open model with first-order absorption kinetics. The plasma concentrations of 2-oxoquazepam were analyzed by a triexponential equation, and pharmacokinetic parameter values of the model equations were estimated by the NONLIN-2 computer program.

Results:

Following drug administration prior to or after sleep, quazepam was rapidly absorbed ($t_{1/2k_a}$ = 0.8 hours). The absorption lag time following nighttime dosing was 1.0 hour as compared to 0.6 hours following morning administration.

For quazepam, the C_{max}, T_{max}, and AUC following nighttime dosing were 32.2 ng/ml, 2.6 hr., and 320.2 hr. - ng/ml respectively; following morning administration, the values were 21.0 ng/ml, 2.5 hr., and 275.6 hr - ng/ml, respectively. The $t_{1/2alpha}$ and $t_{1/2beta}$ following morning administration were 2.1 and 25.0 hours, respectively, and after nighttime dosing were 2.1 and 26.9 hours, respectively. The TBC for the nighttime dose (891 ml/min) was about 17% lower than that for the morning dose (1081 ml/min).

For 2-oxoquazepam, the C_{max}, T_{max}, and AUC values were 13.5 ng/ml, 3.0 hours, and 194.9 hr - ng/ml, respectively, when drug administration occurred just prior to sleep and 9.1 ng/ml, 2.5 hours, and 156.8 hr - ng/ml respectively following morning administration. The $t_{1/2}$ km, $t_{1/2alpha}$, $t_{1/2beta}$ values of 2-oxoquazepam after the morning dose were 1.2, 2.7, 27.9 hours, respectively, and 0.9, 3.6 and 25.8 hours, respectively, following the nighttime dose.

For n-desalkylflurazepam, the mean AUC was 2030.0 hr - ng/ml when the dose was administered prior to sleep and 1468.0 hr - ng/ml following morning administration. The $t_{1/2beta}$ values were 79.3 and 74.1 hours following morning and nighttime administration, respectively.

Reliable and meaningful estimates of C_{max}, T_{max}, and pharmacokinetic parameters (other than elimination half-life) for N-desalkylflurazepam

could not be made since there was a plateauing of the N-desalkylflurazepam plasma levels between 8 and 48 hours.

The data demonstrate that the time of drug administration had no appreciable effect on the pharmacokinetics of the drug and its metabolites, except for the absorption lag time, which was longer following dosing prior to sleep. The effect of drug administration time on quazepam metabolism appeared to be negligible, since the metabolite/quazepam AUC or C_{max} ratios did not vary appreciably between the two times of administration. When drug administration occurred prior to sleep, there was a somewhat increased drug bioavailability since AUC and C_{max} values were consistenly greater than those values observed following morning administration.

These results are summarized in the following tables (XVII-XX).

Conclusion:

From the results of this study, it can be concluded that the pharmacokinetics of quazepam and its major active plasma metabolites (2-oxoquazepam and N-desalkylflurazepam) are not appreciably altered when a single oral dose of quazepam is administered just prior to sleep or during the waking hours. Administration of quazepam before sleep, however, yielded somewhat higher drug bioavailability than the same dose given in the morning. The C_{max} and AUC for quazepam and 2-oxoquazepam and the AUC for N-desalkylflurazepam were consistently higher following the nighttime dose.

Study 8 [redacted]

Secretion of Quazepam in Breast Milk

Objective:

To evaluate the excretion of quazepam and its two major active plasma metabolites (2-oxoquazepam and N-desalkylflurazepam) in the breast milk of lactating females following a single oral dose of quazepam.

Investigator/Institution:

John J. Hanigan, M.D.
[redacted]

Study Design:

Four healthy, nonpregnant lactating female volunteers, 2[illegible]-32 years of age, completed this study. Good health was ascertained through medical history, physical examination, EKG, and routine laboratory tests (hematology, blood chemistries, and urinalysis, including a pregnancy test). Prior to drug administration, each subject agreed to indefinitely stop nursing her infant following the study.

TABLE 5

STUDY NO. [redacted]

TABLE 5

MEAN PLASMA LEVELS, CMAX, TMAX, AND AUC OF QUAZEPAM FOLLOWING SINGLE-DOSE ADMINISTRATION OF A 15 MG QUAZEPAM TABLET JUST PRIOR TO SLEEP AND IN THE MORNING

Mean (% CV)

Parameter / Plasma Levels (ng/ml) Time (hr)	Administration: Prior to Sleep	Administration: Morning
0.0	0.0	0.0
0.5	0.9* (231)	1.5* (108)
1.0	8.2* (159)	9.7 (85)
1.5	19.9* (87)	16.1 (97)
2.0	22.2* (66)	14.8 (70)
3.0	26.3 (31)	16.3 (48)
4.0	23.1 (30)	14.9 (55)
6.0	13.0 (23)	10.2 (59)
8.0	11.0 (29)	8.8 (34)
10.0	7.6 (33)	6.8 (44)
12.0	5.4 (38)	5.3 (42)
14.0	4.6 (51)	4.3 (51)
16.0	4.3 (68)	4.1 (45)
24.0	2.8 (70)	2.9 (55)
48.0	1.3 (54)	1.4* (77)
72.0	0.9* (76)	0.8* (67)
96.0	0.7* (55)	0.6* (78)
120.0	0.6* (62)	0.6* (69)
Cmax (ng/ml)	32.2 (30)	21.0 (63)
Tmax (hr)	2.6 (38)	2.5 (44)
AUC (hr x ng/ml)	320.2 (42)	275.6 (45)

* Individual data at these time points contained values below assay sensitivity limits.

PAGE [redacted]

TABLE 6

MEAN PLASMA LEVELS, CMAX, TMAX, AND AUC OF 2-OXOQUAZEPAM FOLLOWING SINGLE-DOSE ADMINISTRATION OF A 15 MG QUAZEPAM TABLET JUST PRIOR TO SLEEP AND IN THE MORNING

Mean (% CV)

Parameter / Plasma Levels (ng/ml) Time (hr)	Administration: Prior to Sleep	Administration: Morning
0.0	0.0	0.0
0.5	0.5* (85)	0.5* (100)
1.0	2.4* (136)	3.7* (69)
1.5	6.4 (82)	6.3 (85)
2.0	9.0 (61)	6.9 (59)
3.0	11.6 (29)	8.1 (38)
4.0	11.4 (22)	7.5 (42)
6.0	8.3 (21)	5.8 (36)
8.0	7.6 (23)	5.0 (24)
10.0	5.8 (18)	4.2 (24)
12.0	4.8 (18)	3.4 (24)
14.0	4.2 (19)	3.0 (30)
16.0	2.9 (20)	2.3 (21)
24.0	1.9 (21)	1.8 (23)
48.0	0.8* (44)	0.9* (45)
72.0	0.6* (33)	0.6* (37)
96.0	0.4* (50)	0.2* (82)
120.0	0.2* (107)	0.2* (88)
Cmax (ng/ml)	13.5 (21)	9.1 (44)
Tmax (hr)	3.0 (24)	2.5 (40)
AUC (hr x ng/ml)	194.9 (17)	156.8 (24)

* Individual data at these time points contained values below assay sensitivity limits.

TABLE 7

MEAN PLASMA LEVELS AND AUC OF N-DESALKYLFLURAZEPAM FOLLOWING SINGLE-DOSE ADMINISTRATION OF A 15 MG QUAZEPAM TABLET JUST PRIOR TO SLEEP AND IN THE MORNING

Mean (% CV)

Parameter: Plasma Levels (ng/ml) / Time (hr)	Administration: Prior to Sleep	Morning
0.0	0.0	0.0
0.5	0.6* (155)	1.1* (97)
1.0	1.6* (101)	2.6* (78)
1.5	4.6 (58)	6.1 (61)
2.0	6.2 (61)	5.6 (57)
3.0	11.7 (39)	10.0 (36)
4.0	14.7 (26)	11.6 (34)
6.0	16.2 (33)	13.4 (33)
8.0	18.4 (30)	15.7 (26)
10.0	20.4 (25)	14.7 (28)
12.0	21.8 (33)	14.6 (29)
14.0	22.7 (35)	16.0 (25)
16.0	23.1 (30)	16.4 (26)
24.0	21.8 (29)	15.0 (24)
48.0	21.0 (33)	14.3 (29)
72.0	15.9 (43)	12.0 (33)
96.0	13.1 (36)	9.4 (42)
120.0	10.4 (38)	8.5 (49)
AUC (hr x ng/ml)	2030.0 (32)	1468.0 (28)

* Individual data at these time points contained values below assay sensitivity limits.

TABLE 8

MEAN PHARMACOKINETIC PARAMETERS OF QUAZEPAM, 2-OXOQUAZEPAM, AND N-DESALKYLFLURAZEPAM AFTER SINGLE ORAL ADMINISTRATION OF A 15 MG QUAZEPAM TABLET IN THE MORNING OR JUST PRIOR TO SLEEP

Mean (% CV)

Quazepam	$t_{1/2}\alpha$	$t_{1/2}\beta$	$t_{1/2}ka$	t_{lag}	TBC
Morning	2.1 (52)	25.0 (30)	0.9 (58)	0.6 (35)	1081 (42)
Sleep	2.1 (37)	26.9 (25)	0.7 (51)	1.0 (49)	891 (35)

2-oxoquazepam	$t_{1/2}\alpha$	$t_{1/2}\beta$	$t_{1/2}ka$		
Morning	2.7 (32)	27.9 (18)	1.2 (46)	—	—
Sleep	3.6 (25)	25.8 (26)	0.9 (34)	—	—

N-desalkylflurazepam		$t_{1/2}\beta$			
Morning	—	79.3 (29)	—	—	—
Sleep	—	74.1 (32)	—	—	—

The $t_{1/2}\alpha$, $t_{1/2}\beta$, $t_{1/2}ka$, and $t_{1/2}ka$ are half-lives (hours) of distribution, elimination, absorption, and formation phases, respectively; t_{lag} is absorption lag time (hours); and TBC is total body clearance (ml/min).

STUDY [redacted]

STUDY NO. [redacted]

TABLE 8

MEAN PHARMACOKINETIC PARAMETERS OF QUAZEPAM, 2-OXOQUAZEPAM, AND N-DESALKYLFLURAZEPAM
AFTER SINGLE ORAL ADMINISTRATION OF A 15 MG QUAZEPAM TABLET
IN THE MORNING OR JUST PRIOR TO SLEEP

Mean (% CV)

Quazepam	$t_{\frac{1}{2}}\alpha$	$t_{\frac{1}{2}}\beta$	$t_{\frac{1}{2}}ka$	t_{lag}	TBC
Morning	2.1 (52)	25.0 (30)	0.9 (58)	0.6 (35)	1081 (42)
Sleep	2.1 (37)	26.9 (25)	0.7 (51)	1.0 (49)	891 (35)
2-oxoquazepam	$t_{\frac{1}{2}}\alpha$	$t_{\frac{1}{2}}\beta$	$t_{\frac{1}{2}}ka$		
Morning	2.7 (32)	27.9 (18)	1.2 (46)	—	—
Sleep	3.6 (25)	25.8 (26)	0.9 (34)	—	—
N-desalkylflurazepam		$t_{\frac{1}{2}}\beta$			
Morning	—	79.3 (29)	—	—	—
Sleep	—	74.1 (32)	—	—	—

The $t_{\frac{1}{2}}\alpha$, $t_{\frac{1}{2}}\beta$, $t_{\frac{1}{2}}ka$, and $t_{\frac{1}{2}}ka$ are half-lives (hours) of distribution, elimination, absorption, and formation phases, respectively; t_{lag} is absorption lag time (hours); and TBC is total body clearance (ml/min).

STUDY [redacted]

Each subject received a single oral 15 mg quazepam (FMR No. [redacted] Batch No. 12071-97 tablet). Blood samples were collected prior to and at 1, 2, 3, 4, 6, 8, 12, 24, 36, and 48 hours after drug administration. Breast milk was collected prior to drug administration and then at intervals of 0 to 2, 2 to 4, 4 to 6, 6 to 8, 8 to 12, 12 to 24, 24 to 36 to 48 hours after dosing. Milk from each breast during a collection interval was pooled. Volumes of breast milk obtained were used to calculate the total amount of quazepam and its two metabolites that were excreted through each time point. Breast milk and blood samples were analyzed by GC methods to determine levels of quazepam and its metabolites.

A slight modification of the plasma assays of quazepam and 2-oxoquazepam was necessary to analyze the compounds in breast milk due to the interference of milk lipids in the chromatographic procedures. Validation of this analytical method was found adequate with linearity observed over the concentration range [redacted] to [redacted] ng/ml, sensitivity to 1.5 ng/ml, and reproducibility within 3.5% (CV) for 5 determinations of 3 concentrations of each of the two compounds.

Results:

Breast milk levels of quazepam were considerably greater than corresponding plasma levels for the first 12 hours postdosing; for 2-oxoquazepam, this was observed for the first eight hours. Through 48 hours, 11.6 mcg of quazepam and 4.0 mcg of 2-oxoquazepam were found in the breast milk, respectively representing only 0.08% and 0.02% of the administered quazepam dose.

Breast milk levels of N-desalkylflurazepam were less than one-tenth of corresponding plasma levels. Through 48 hours, only 1.0 mcg (0.009% of the administered quazepam dose) was found in the breast milk.

Plasma and breast milk data are summarized in the following table (XXI).

Conclusions:

There is excretion of quazepam and its two major active metabolites into breast milk. Through 48 hours following single 15 mg dose administration, total excretion of quazepam and its two active plasma metabolites in breast milk was only 0.11% of the administered quazepam dose.

Labeling

Labeling was found acceptable. The pharmacokinetic parameters were adequately expressed as was the fact that the elimination half-life of N-desalkylflurazepam in geriatric patients is about twice that of young adults. The normal dosage for adults is 30 mg before retiring with 15 mg sufficing in some patients, while elderly or debilitated patients should have therapy initiated at 15 mg with [redacted] mg being the desired dose in some cases. Quazepam and its major metabolites are excreted in the milk of lactating women, and the labeling cites that this drug should not be given to nursing mothers.

TABLE 5

MEAN (N=4) PLASMA AND BREAST MILK LEVELS (NG/ML) OF QUAZEPAM AND ITS MAJOR ACTIVE METABOLITES FOLLOWING ADMINISTRATION OF A SINGLE 15 MG QUAZEPAM TABLET

Mean (% CV)

Time (hr)	Quazepam		2-oxoquazepam		N-desalkylflurazepam	
	Plasma	Milk	Plasma	Milk	Plasma	Milk
0	0.0	0.0	0.0	0.0	0.0	0.0
1	12.8 (68)	—†	3.8 (66)	—†	4.9 (67)	—†
2	17.4 (70)	65.3 (97)	8.9 (63)	21.6 (87)	11.4* (69)	1.1* (82)
3	19.2 (17)	—†	9.6 (30)	—†	15.2 (39)	—†
4	11.1 (29)	85.9 (102)	6.7 (30)	23.6 (53)	17.3 (34)	1.6* (38)
6	7.6 (22)	56.2 (105)	5.2 (31)	15.4 (43)	18.9 (34)	1.8* (58)
8	4.9 (28)	31.3 (95)	3.4 (28)	7.8 (51)	19.7 (24)	1.8* (48)
12	2.5 (18)	9.9 (102)	2.0 (13)	3.0 (96)	19.3 (24)	1.8* (40)
24	1.6 (26)	2.7 (58)	1.2 (8)	1.4* (28)	17.1 (28)	1.5* (26)
36	1.5 (19)	2.9 (69)	1.1 (16)	1.4* (14)	20.0 (17)	1.8* (31)
48	0.8* (18)	2.3* (49)	0.8* (18)	0.9* (53)	16.1 (16)	1.4* (16)

* Individual data at these time points contained values below assay sensitivity limits.

† Milk was not collected at these time points.

Dissolution:

Corcition for Dissolution Testing of 15 mg and 30 mg Quazepam Tablets

USP XX Paddle Stirrer, Apparatus 2 operated at 50 rpm
Medium: Dilute 400 ml USP ethanol to 1000 ml with water
Volume: 900 ml at 37 ± 0.5°C
Dissolution Rate: Q = 80% in 30 minutes
Sample Analysis: UV absorption

At an earlier time, apparently EDRO expressed concern that the hydroalcoholic dissolution media will make calibration difficult and that water alone would be preferred.

In a solubility profile (pg. [redacted] Vol. no [redacted], the solubility of quazepam in water is listed as being [redacted] mg/ml; in 0.1 N HCl its solubility is [redacted] ng/ml, and the compound was found to be unstable in 0.1N NaOH.

A complete pH-dissolution profile was not submitted nor was the ionization constant for the compound (a weak base) given. It is possible that a more acceptable aqueous-buffer or aqueous-surfactant dissolution media could be found.

The addition of the dye appears to slow dissolution and increase % CV (tablet - to - tablet variability). The tablets fell within the USPXX Stage 2 Accceptance Table.

[redacted] Dissolution data was not supplied for Quazepam [redacted] mg tablets containing

Comments:

1. With quazepam suspension as the reference dosage form, there were no substantial pharmacokinetic differences among the suspension, capsule and tablet formulations when subjects were administered 15 mg doses of the drug.

2. In geriatric patients, the elimination half-life of N-desalkylflurazepam is about twice that of young adults.

3. The tablet formulation was found to be dose proportional over the range of [redacted] mg to [redacted] mg.

4. a. The dissolution testing conducted by Schering Corporation on its quazepam is not acceptable. Use of organic solvents as dissolution media is to be avoided if possible. The firm should agree to examine the potential for either an aqueous-buffer dissolution media or the incorporation of (a) solubilizing surfactant(s) in an aqueous dissolution media as a condition for approval. (Phase IV Study). A pH - dissolution profile should be generated.

   b. Dissolution profile data should be provided for Quazepam [redacted] mg tablets containing [redacted]

Recommendation:

1. The bioavailability studies found in volume no. [redacted] (and complemented by volume nos. [redacted] nd [redacted] (submission dated April 2, 1982) conducted by Schering Corporation on quazepam have been found acceptable by the Division of Biopharmaceutics.

2. The dissolution testing conducted by Schering Corporation on its quazepam 15 mg and [redacted] mg tablets is not acceptable. See comment #4.

   Until the potential for using an aqueous-buffer or aqueous - surfactant dissolution media has been examined, the dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml of a solution composed of 400 ml USP ethanol diluted to 1000 ml with water at 37°C using USP Apparatus II at 50 rpm. The test product should meet the following specification:

   [redacted] = [redacted] in [redacted] minutes

3. Based on the results of the submitted bioavailability studies, the application is acceptable to the Division of Biopharmaceutics if the firm agrees to further dissolution testing as outlined in comment #4.

Karen B. Oseekey
Karen B. Oseekey
Pharmacokinetics Branch

RD INITIALED BY PURICH
FT INITIALED BY PURICH Edward D. Purich

RD:cs:4-25-83[redacted]:FT:kak:4/26/83

cc: Orig., HFN-120, HFN-525 (Oseekey), Chron. (Bette), Chron, (Pat), Drug, Division, and Review File.

Dissolution Profiles of Quazepam Tablets
Number of Tablets Tested 12

Time (min)	Test Product * 15 mg Quazepam Tablet FMR No. 79691D-02		
	Mean% Dissolved	Range	SD**
7.5	77		12
15	95		8
22.5	100		6
30	103		5
45	105		3
60	107		2

*Differ from product described in sections 6, 7, and 8 of this NDA only with respect to absence of dye. The NDA formulations contain [redacted] and [redacted] mg of [redacted] for the 15 mg and [redacted] mg tablets respectively.

**SD = standard deviation.

Dissolution Profile of Quazepam Tablet
Containing [redacted]
Number of tablets tested 12

15 mg Quazepam Tablet
FMR No. [redacted]
Batch No 12071-97

Time (min)	Mean% Dissolved	Range	SD	%CV*
7.5	69		16	23
15	88		15	17
22.5	94		12	13
30	98		9	9
45	99		8	8
60	100		8	8

*CV = Coefficient of variation

NDA 18 708

NDA 18-708

DEC -3 1991

Wallace Laboratories
Division of Carter-Wallace
Attention: Monroe I. Klein, Ph.D.
301B College Road East
Princeton, New Jersey 08540

Dear Dr. Klein:

Reference is made to your new drug application submitted pursuant to section 505(b) of the Federal Food, Drug and Cosmetic Act for Doral (quazepam) Tablets, 7.5 mg and 15 mg.

There has been much concern recently about the misuse of benzodiazepine hypnotics, particularly the use of these drugs for longer durations than is appropriate and their use in patients not adequately evaluated for the presence of underlying psychiatric or physical disorders that are manifested by insomnia. Contributing to the overall problem of hypnotic misuse is a tendency for physicians to write individual scripts for larger quantities of hypnotics than are required. There has also been concern that patients have not been adequately informed about the risks and benefits of these products.

The FDA has consulted widely on this matter and concluded that relatively extensive changes should be made in the way that benzodiazepine drug products are labeled, packaged, and distributed. Consequently, we are asking the manufacturers of benzodiazepine products marketed specifically as hypnotics 1) to make a series of changes in the text of their professional product labeling, 2) to provide supplies of their product intended for distribution to ambulatory, non-institutionalized patients in unit of use packages containing no more than 10 night's supply, and 3) to attach a patient package insert (PPI) to these units of use packages. We recognize that some time may elapse before the unit of use packaging can be implemented; in the interim, the PPI should be distributed to retail pharmacies for distribution to patients. Finally, Dear Dr. Letters announcing these changes should be issued.

The requested labeling changes and the PPI for all products share common features. When necessary, however, language specific to a particular product's risks and benefits is proposed.

For Doral (quazepam), we ask that you make the following changes:

Clinical Pharmacology

We are asking manufacturers of benzodiazepine hypnotics to include all information supportive of the hypnotic efficacy of these products in this section of labeling. Your currently approved Clinical Pharmacology section has some information of this nature, and your Indications section also contains some description of the data supportive of hypnotic efficacy. Consequently, we ask that you combine all of this information into a subsection of Clinical

Pharmacology that summarizes in one place the clinical trials providing support for the hypnotic efficacy of Doral.

Indications and Usage

We have prepared the following standard language for hypnotic Indications sections that emphasizes the importance of short-term use and the careful evaluation of patients. We ask that you adopt this language verbatim for this section, as follows:

> 'Doral is indicated for the short-term treatment of insomnia (generally 7-10 days). Use for more than 2-3 weeks requires complete reevaluation of the patient (See Warnings).
>
> Prescriptions for Doral should be written for short-term use (7-10 days) and it should not be prescribed in quantities exceeding a 1-month supply.'

Warnings

We have prepared the following standard language for hypnotic Warnings sections that emphasizes the importance of initial and continued evaluation of patients with insomnia, the importance of finding the lowest effective dose, and the need to pay particular attention to the emergence of abnormal thinking and behavior changes in patients being treated with benzodiazepine hypnotics. We ask that you adopt this language verbatim and add it as the initial information in this section, as follows:

> 'Sleep disturbance may be the presenting manifestation of a physical and/or psychiatric disorder. Consequently, a decision to initiate symptomatic treatment of insomnia should only be made after the patient has been carefully evaluated.
>
> The failure of insomnia to remit after 7 to 10 days of treatment may indicate the presence of a primary psychiatric and/or medical illness.
>
> Worsening of insomnia or the emergence of new abnormalities of thinking or behavior may be the consequence of an unrecognized psychiatric or physical disorder. These have also been reported to occur in association with the use of Doral.
>
> Because some of the important adverse effects of Doral appear to be dose related (see Precautions and Dosage and Administration), it is important to use the smallest possible effective dose. Elderly patients are especially susceptible.
>
> A variety of abnormal thinking and behavior changes have been reported to occur in association with the use of benzodiazepine hypnotics. Some of these changes may be characterized by decreased inhibition, e.g.,

aggressiveness and extroversion that seem out of character, similar to that seen with alcohol and other CNS depressants (e.g.,sedative/hypnotics). Other kinds of behavioral changes can also occur. for example, bizarre behavior, agitation, hallucinations, depersonalization. In primarily depressed patients, the worsening of depression, including suicidal thinking, has been reported in association with the use of benzodiazepines.'

It can rarely be determined with certainty whether a particular instance of the abnormal behaviors listed above is drug induced, spontaneous in origin, or a result of an underlying psychiatric or physical disorder. Nonetheless, the emergence of any new behavioral sign or symptom of concern requires careful and immediate evaluation.

The three paragraphs that are contained in the currently approved Warnings section should follow this new information.

Precautions

The information that is currently in the Information for Patients subsection of this section should be deleted and replaced by a reference to the Doral PPI to be included as part of the package insert and distributed to patients.

PPI

Attachment 1 to this letter is our proposal for a PPI for Doral. This should be adopted verbatim and should become part of the package insert for physicians as well as being distributed separately to patients. Until that unit of use packaging is available (see below), the PPI should be distributed to the level of distribution where drug is delivered to individual patients (e.g., ambulatory outpatient institutional pharmacies, retail pharmacies, group health organization pharmacies, etc.) in sufficient quantities to allow delivery of the PPI to every individual user.

Unit of Use Packaging

You should immediately undertake to manufacture unit-of-use packaging for Doral that will provide for no more than a 10-day supply. The new package should be designed to allow the physical incorporation of the PPI within or upon the unit of use package. When this packaging is ready for distribution, it should become the only form in which Doral is distributed to patients who are not institutionalized.

Time of Implementation

Your firm should immediately make the proposed labeling changes and prepare the requested PPI in final printed format (N.B. we suggest that printing be limited to allow for editing). We request that you submit both the revised final printed labeling and the PPI for our review within a period of no more than 30 days of the date of this letter. At the same time, we request that you submit a schedule for the timely implementation of the unit of use packaging.

Conclusions

The agency is mindful of the effort and cost that your firm will need to expend in the course of adopting the requested changes. The cost notwithstanding, we believe that the changes are of great importance to the safe and prudent use of hypnotics and we trust, therefore, that you will cooperate fully in seeing that they are made expeditiously.

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

Sincerely yours,

12/3/91

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

ATTACHMENT

CC: ORIG NDA
HFD-120
HFD-120/Leber
HFD-120/DCollins/TLaughren:11/15/91
HFD-120/MMille:11/15/91;12/3/91
HFD-632
GCF-1/AWion
DT:11/8/91/gt
REVISED: Leber/Laughren/12/3/91;AWion/12/3/91
FT:11/14/91/gt;12/3/91/mjm
DOC# F:\MILLE\N18708.123

FPL CHANGE REQUEST

ATTACHMENT 1

Patient Package Insert for Doral

INFORMATION FOR THE PATIENT

INTRODUCTION

Doral is intended to help you sleep. It is one of several benzodiazepine sleeping pills that have generally similar properties. Anyone who is considering using one of these drugs should be aware of both their benefits and several important risks and limitations, including diminishing effectiveness with continued use and the possible development of dependence (addiction) and possibly mental changes particularly when the drugs are used for more than a few days to a week. This patient information statement is intended to provide you with knowledge about this class of medications in general and about Doral in particular that will be useful to guide you in the safe use of this product, BUT IT SHOULD NOT REPLACE A DISCUSSION BETWEEN YOU AND YOUR PHYSICIAN ABOUT THE RISKS AND BENEFITS OF DORAL.

This leaflet will focus on the beneficial and adverse effects of all members of this class of drugs, as well as some specific information for Doral. There are some differences among these drugs, and your physician may wish to discuss any specific advantages and disadvantages of particular members of this drug class with you.

EFFECTIVENESS OF BENZODIAZEPINE HYPNOTICS

Benzodiazepine sleeping pills are effective and relatively free of serious problems when they are used for short-term management of insomnia. Insomnia is not always the same. It may be reflected in difficulty in falling asleep, frequent awakening during the night, and/or early morning awakening. Insomnia is often transient in nature, requiring only brief treatment with hypnotics. Use for more than a short while requires discussion with your physician about the risks and benefits of prolonged use.

SIDE EFFECTS

Common Side Effects

The most common side effects of benzodiazepine sleeping pills are related to the ability of the medications to make you sleepy: drowsiness, dizziness, lightheadedness, and difficulty with coordination. Users must be cautious about engaging in hazardous activities requiring complete mental alertness, e.g., operating machinery or driving a motor vehicle. Do not take alcohol while using Doral. Benzodiazepine sleeping pills should not be used with other medications or substances that may cause drowsiness, without discussing said use with your physician.

How sleepy you are the day after you use one of these medications depends on your individual response and on how quickly the product is eliminated from your body. Doral is one of the more slowly eliminated benzodiazepine sleeping pills, and it is associated with next day sedative effects. The larger the dose, the more

likely an individual will experience next day residual effects such as drowsiness. For this reason, it is important to find the lowest effective dose, for each individual patient. Benzodiazepines that are eliminated rapidly tend to cause less next day drowsiness but may cause more withdrawal problems the day after use (see below).

Special Concerns

Memory Problems

All benzodiazepine sleeping pills can cause a special type of amnesia in which a person may not recall events occurring for some period of time, usually several hours, after taking such a medication. This is ordinarily not a problem, since the person taking a sleeping pill intends to be asleep during this vulnerable period of time. It can be a problem when sleeping pills are taken to induce sleep while traveling, such as during an airplane flight, because the person may awake before the effect of the medication is gone. This has been called "traveler's amnesia."

Tolerance/Withdrawal Phenomena

Some degree of tolerance or adaptation to the sleep inducing effects of these medications may develop after nightly use for more than a few weeks and there may be a degree of dependence that develops. For the benzodiazepine sleeping pills that are eliminated quickly from the body a relative deficiency of the medication may occur at some point in the interval between each night's use. This can lead to (1) increased wakefulness during the last third of the night, and (2) the appearance of increased signs of day-time anxiety or nervousness.

There can be more severe 'withdrawal' effects when a benzodiazepine sleeping pill is stopped. Such effects can occur after discontinuing these medications following use for only a week or two, but may be more common and more severe after longer periods of continuous use. One type of withdrawal phenomenon is the occurrence of what is known as 'rebound insomnia; that is, on the first few nights after the medication is stopped, insomnia is actually worse than before the sleeping pill was given. Other withdrawal phenomena following abrupt stopping of benzodiazepine sleeping pills range from mild unpleasant feelings to a major withdrawal syndrome that may include abdominal and muscle cramps, vomiting, sweating, tremor, and rarely, convulsions. These more severe withdrawal phenomena are very uncommon.

Dependence/Abuse Phenomena

All benzodiazepine sleeping pills can cause dependence (addiction), especially when used regularly for more than a few weeks or at higher doses. Some people develop a need to continue taking these medications, either at the prescribed dose or at increasing doses, not so much for continued therapeutic effect, but rather, to avoid withdrawal phenomena and/or to achieve nontherapeutic effects. Individuals who have been dependent on alcohol or other drugs may be at particular risk of becoming dependent on drugs in this class, but all people appear to be at some risk. This possibility must be considered before extending the use of these medications for more than a few weeks.

Mental and Behavioral Changes

A variety of abnormal thinking and behavior changes have been reported to occur in association with the use of benzodiazepine sleeping pills. Some of these changes are like the release of inhibition seen in association with alcohol, e.g., aggressiveness and extroversion that seem out of character. Others, however, can be more unusual and more extreme such as confusion, bizarre behavior, agitation, hallucinations, depersonalization, and worsening of depression, including suicidal thinking. It is rarely clear whether such events are induced by the drug being taken, are caused by some underlying illness or are simply spontaneous happenings. In fact, worsened insomnia may in some cases be associated with illnesses that were present before the medication was used. In any event, the most important fact is to understand that regardless of the cause, users of these medications should promptly report any mental or behavioral changes to their doctor.

Effects on Pregnancy

Certain benzodiazepines have been linked to birth defects when administered during the early months of pregnancy. In addition, the administration of benzodiazepines during the last weeks of pregnancy has been associated with sedation of the fetus. Consequently, the use of Doral should be avoided at any time during pregnancy.

SAFE USE OF BENZODIAZEPINE HYPNOTICS

To assure the safe and effective use of Halcion, you should adhere to the following cautions:

1. Doral is a prescription medication and, therefore, should be used only as directed by your doctor. Follow your doctor's advice about how to take it, when to take it, and how long to take it. As with other prescription medication, Halcion should be taken only by the individual for whom it is prescribed.

2. Do not extend your use of Doral beyond 7-10 days without first consulting with your physician.

3. If you develop any unusual and disturbing thoughts or behavior during treatment with Doral, you should discuss such problems with your physician.

4. Inform your physician about any alcohol consumption and medicine you are taking now, including drugs you may buy without a prescription. Do not use alcohol while taking Doral.

5. Do not take Doral in circumstances where a full night's sleep and elimination of the drug from the body are not possible before you would again need to be active and functional, e.g., an overnight flight of less than 7-8 hours, since amnestic episodes have been reported in such situations.

6. Do not increase the prescribed dose except on the advice of your physician.

7. Until you experience how this medication affects you, do not drive a car or operate potentially dangerous machinery, etc.

8. Be aware that you may experience an increase in sleep difficulties (rebound insomnia) on the first night or two after discontinuing Doral.

9. 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. The use of Doral should be avoided at any time during pregnancy.

END OF TEXT

NDA 18-708

Quazepam

SBA

SUMMARY BASIS OF APPROVAL

NDA 18-708

Drug Generic Name: quazepam

Applicant: Schering Corporation
60 Orange Street
Bloomfield, New Jersey 07003

Drug Trade Name: to be determined

I. Indications for Use: hypnotic agent

II. Dosage form, Route of Administration and Recommended Dosage:

tablets, 15 mg; oral

II. Manufacturing and Controls

A. Manufacturing and Controls

The firm has adequately described the synthesis, manufacture, and test procedures for the drug to ensure its identity, strength, quality and purity.

B. Stability Studies

The firm submitted adequate data to support the proposed one year expiration date. Appropriate committments have been made for the continued monitoring of representative samples of the marketed drug including subpotency withdrawal statement.

C. Methods of Validation

The assay method has been validated and is considered adequate for both control and regulatory analysis.

D. Labeling

The labeling contains the required technical information.

E. Establishment Inspection

Schering's facilities were recently inspected and found to be in compliance with the regulations on current good manufacturing practices for the manufacture of this drug.

F. Environmental Impact Analysis Report

A statement that the manufacture of this drug will be without significant impact or the environment is included in the firm's submission. The report is regarded as satisfactory and no further considerations are necessary for the approval of this application.

cc:
HFN-120/Iliev
Shultz/init/8/31/84
rd/mlm/8/31/84/FT/9/4/84
Doc 1725C page 25

REVIEW OF CHEMISTRY AND MANUFACTURING CONTROL

MAY - 9 1986

NDA #18-708

Sponsor: Schering Corporation
Address: Galloping Hill Road
Kenilworth, NJ 07033

Division: HFN-120
Chemist Review: #1
Reviewing Chemist: Alex Post
Date Received: 5/1/86
Date Completed: 5/2/86
Received CDB: 4/28/86

Product Name:

Proprietary:
Non-Proprietary: Quazepam

Dosage Form(s) and Route(s) of Administration: Tablets (15 mg); oral

Pharmacological Category and/or Principal Indication: Hypnotic

Structural Formula & Chemical Name:

Initial Submission: April 5, 1982

Amendments: 4/25/86

Remarks:

Final printed labels for bottle of 14 (professional sample), bottles of 100 and 500 units, backing for 3 (professional sample) and carton for 3 (professional sample) have been submitted and are technically correct.

The package insert has also been submitted and the description information is technically correct and has been revised as requested in the Agency's letter of 12/27/85 (inclusion of inactive ingredients).

Conclusions and Recommendations:

I recommend that the labels be approved and the insert accepted (description only).

Alex Post

Alex Post, Reviewing Chemist

cc: ORIG:NDA
HFN-102/CKumkumian
HFN-120
HFN-120/APost/5/2/86
INIT:RCShultz/5/2/86
ft/evh/5/5/86
CSO:JCreamer
DOC#16630

NDA
~~IND~~ # 18-708

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

Review of Chemistry and Manufacturing Controls

Applicant: Schering Corporation
Sponsor:
Address: Bloomfield, N.J. 07003

Division: HFD-120
Chemist Review # 1
Reviewing Chemist: V.Iliev, Ph.D.

Date Completed: April 23, 1982

Product Name(s):

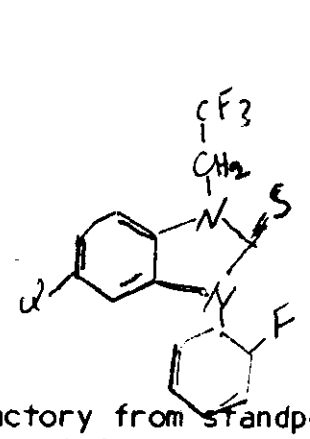
Proprietary: Quazepam Sch 16134
Non-proprietary:
Compendium:
USAN:
Code name/number:

Dosage Form(s) and Route(s) of Administration: Oral, Tablets

Pharmacological Category and/or Principal Indication: Hypnotic

Structural Formula & Chemical Name:

7-chloro-5(2-fluorophenyl)1,3-dihydro-1-(2,2,2-trifluoroethyl)
2H-1,4,benzodiazepine, 2-thione



Initial Submission: April 5, 1982
Amendment(s):
Related Documents: D.M.F. IND

Remarks:

Conclusions and Recommendations: Satisfactory from standpoint of controls pending satisfactory validation.

V. Iliev
Chemist

cc: Orig. IND
HFD-102/Kumkumian (only Chem. Revs. #1)
HFD-120
HFD-120/Iliev/4/23/82
RD init by: RCShultz/4/26/82
FT/lca/5/3/82
Doc.#2257B

1. Components - Satisfactory listed.

2. Composition -

	mg/tablet	Representative Batch Formula g/100,000 Tablets
Quazepam, Micronized	30.0	3,000*

*

Approximate Tablet Wt. ____ ____ _____

Approximate Batch Wt.

* Up to % overcharge may be added.

** The amount of magnesium stearate may vary from mg to mg per tablet with compensating adjustments made in the tablet weight or amount of lactose used or both.

*** Sufficient amounts of purified water are added as required for the manufacturing process.

3. Facilities - Satisfactory.

4. Personnel: Satisfactory.

5. Synthesis:

6. Raw Material Controls a) New drug substance - Satisfactory controlled.

7. Other Firms -

   D.M.F.

8. Manufacturing Processing - Satisfactory described.

9. Container - H.D.P.E., metal cap, pulp liner.

10. Packaging and Labeling - Satisfactory.

11. Laboratory Controls (Finished dosage form) - Dissolution in related compound, T.L.C., H.P.L.C.

12. Control numbers are assigned.

13. Stability - 12 months stability data, H.P.L.C.

Labeling - Draft labeling is attached.

Environmental Impact Analysis - No significant environmental impact is foreseen.

CHEMIST'S REVIEW
(If necessary, continue any item on 8" x 10½" paper. Key continuation to item by number.)

1. ORGANIZATION: RD 120	2. NDA NUMBER: 18708
3. NAME AND ADDRESS OF APPLICANT (City and State): Schering Corporation, Bloomfield N.J. 07003	4. AF NUMBER
	5. SUPPLEMENT (S) — NUMBER(S) / DATE(S)
6. NAME OF DRUG: Clorazepam	7. NONPROPRIETARY NAME
8. SUPPLEMENT(S) PROVIDES FOR: Inspectional Report	9. AMENDMENTS AND OTHER (Reports, etc.) DATES
10. PHARMACOLOGICAL CATEGORY: hypnotic	11. HOW DISPENSED: ☒ RX ☐ OTC
12. RELATED IND/NDA/DMF(S)	
13. DOSAGE FORM (S): Tablet	14. POTENCY (Iso)
15. CHEMICAL NAME AND STRUCTURE	16. RECORDS AND REPORTS — CURRENT: ☐ YES ☐ NO; REVIEWED: ☐ YES ☐ NO

17. COMMENTS

Memo from Manufacturing Review Branch dated August 16, 1982 as to compliance with G.M.P. for:

18. CONCLUSIONS AND RECOMMENDATIONS

Satisfactory from standpoint of Controls

19. REVIEWER		
NAME: V. Klein	SIGNATURE: V. Klein	DATE COMPLETED: 8-30-82

DISTRIBUTION ☐ ORIGINAL JACKET ☐ REVIEWER ☐ DIVISION FILE

FORM FDH 2266 (7/75) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED. 1

DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Food and Drug Administration
Rockville MD 20857

DATE : 8/16/82

FROM : Manufacturing Review Branch (HFD-324)
Division of Drug Manufacturing

SUBJECT : APPROVABLE 18-708 BRAND & GRAZEPAN

TO : Director
Division of NEUROPHARM (HFD-120)
Drug Products

Attn: ILIEV

APPLICANT: SCHERING CORP

We have evaluated the operations of the indicated firms as they relate to compliance with Current Good Manufacturing Practice Regulations (21 CFR 211) with the exception of expiration dating (211.137) and stability testing (211.166) for the referenced application(s). Since you evaluate the applicant submission of stability data and proposed expiration date, you should made the determination that the stability testing is adequate to support the proposed expiration date. If you desire, you can include appropriate references to 211.137 and 211.166 as deviations directly into your non-approvable letter if you conclude the stability testing is inadequate. Otherwise, we conclude there is no reason to withhold approval of the subject application(s) insofar as CGMP compliance of this/these firm(s) is concerned for the type of operations as specified in this/these pending application(s).

Our evaluation is based in part on Establishment Inspection and Quality Assurance Profile information.

Seymour Fishman

NWK-DO
HFD-616
FT/lca/8/11/82

CHEMIST'S REVIEW

(If necessary, continue any item on 8½" x 10½" paper. Key continuation to item by number.)

1. ORGANIZATION: HFD-120

2. NDA NUMBER: 18-708

3. NAME AND ADDRESS OF APPLICANT (City and State)

Schering Corporation
Bloomfield, New Jersey 07073

4. AF NUMBER

5. SUPPLEMENT (S)

NUMBER(S)	DATE(S)

6. NAME OF DRUG: Quazepam

7. NONPROPRIETARY NAME

8. SUPPLEMENT(S) PROVIDES FOR:

Validation Report

9. AMENDMENTS AND OTHER (Reports, etc.) DATES

July 28, 1982

10. PHARMACOLOGICAL CATEGORY: hypnotic

11. HOW DISPENSED: ☒ RX ☐ OTC

12. RELATED IND/NDA/DMF(S)

13. DOSAGE FORM (S): Tabs

14. POTENCY (les)

15. CHEMICAL NAME AND STRUCTURE

16. RECORDS AND REPORTS

CURRENT: ☐ YES ☐ NO

REVIEWED: ☐ YES ☐ NO

17. COMMENTS

The proposed methodology was found satisfactory by the New York Regional Laboratory and the Washington Laboratory.

HFD-120
HFD-120/VIliev/8/6/82
RDinit. RSilk for RCShultz/8/6-82

18. CONCLUSIONS AND RECOMMENDATIONS

Approval recommended from standpoint of controls.

19. NAME: Venelin Iliev, Ph.D.

REVIEWER SIGNATURE: [signature]

DATE COMPLETED: 8-6-82

DISTRIBUTION: ☐ ORIGINAL JACKET ☐ REVIEWER ☐ DIVISION FILE

FORM FDA 2766 (7/75) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : Laboratory Operations Branch/DFS/EDRO
Attn: Salvatore J. Pinella (HFO-610)

DATE: July 28, 1982

For forwarding to: ( )HFD-530
(X)HFD-120

FROM : Research Coordinator
New York Regional Laboratory (HFR-2620)

SUBJECT: IND

PRODUCT: Quazepam Tabs

Rec'd
8/4/82
SJP

FIRM: Schering Corp.
Kenilworth, N.J. 07033

No problems were encountered with the proposed method. All analytical results appear to be satisfactory.

WILLIAM M. PLANK

WILLIAM M. PLANK

cc: HFR-2660 : File 463: 311
Lab G. 40 hours 4 exams, Analyst L. Valenti
Lab H (Monitor)
HFR-2620