MORS

NOV 30 1992

Review and evaluation of clinical data

NDA	19-908
Sponsor	Lorex
Drug	Ambien®
Drug class	1-C
Proposed indications	Sedative-hypnotic
Material reviewed	General Correspondence (1 vol)
Date of correspondence	Nov 19, 1992
Date received	Nov 20, 1992
Safety review date	N/A
Related INDs	/

Background

On Nov 16, 1992, at Agency request, the sponsor submitted a listing of patients reporting psychiatric/neurological AEs such as depression, amnesia, and hallucinations. The sponsor has extracted narrative descriptions of these events from all CRFS in the Lorex data base, and submits them herewith. A similar process has been undertaken with respect to the LERS data base and will be submitted when available - probably within the next 30 days.

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Clinical experience The material submitted consists of a line listing of 111 subjects (76 males, 35 females) participating in 23 studies who reported one or more AEs of the type described above (total number of reports: 186. The line-listing is followed by one-page transcriptions of all entries in the CRFs bearing on the particular AE; these are organized by study.

The Population.

1. The distribution of subjects reporting one or more psychiatric symptoms, by type of study and gender, is shown below. Figures in brackets are the total numbers of subjects at risk and the total numbers of studies in the NDA.

Type of study	# of studies	Males	Females	Total (%)
In NDA:				
Clin Pharm [N=240]	9 [12]	48	-	48 (20%)
Controlled [576]	4 [6]	9	7	16 (2.8%)
Open [N=242]	2 [2]	12	17	29 (12.0%)
Not included in NDA:				
Clin Pharm	3	2	1	
Controlled	5	5	10	
Totals	23	76	35	

2. The following table gives the distribution of subjects by the lowest dose at which they reported one of the target AEs.

	Male	Female
60 mg	1	-
40 mg	13	-
30 mg	2	-
20 mg	25	5
15 mg	14	19
10 mg	17	8
7.5 mg	2	-
5 mg	2	3
Totals	76	35

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3. The distribution of subjects, by type of AE, was as follows:

	Male	Female
Amnesia	12	18
Euphoria	28	1
Depression	6	8
Hallucinations	9	1
All other	25	5

The AEs.

1. **Amnesia.** The distribution of amnesia/memory loss, by dose and gender, is as follows:

	Male	Female
40 mg	1	-
20 mg	7	2
15 mg	4	12
10 mg	-	4

The 4 cases of amnesia/memory loss reported at the currently recommended dose (10 mg) are summarized briefly.

LSH /33 - 56 y/o female, amnesic for last 20 min before bedtime.
LSH /02 - 57 y/o female, complaining of slow recall in the morning following dosing.
LSH61/16 - 25 y/o female, amnesic for visit to bathroom immediately before lights out.
LSH12/Mendels - #36 - 33 y/o female, with a single complaint of mild memory impairment after 65 nights of open-label treatment.

2. **Euphoria.** All reports of euphoria occurred in connection with daytime dosing in Clinical Pharmacology trials; 9/29 reports were at a dose ≤10 mg.

3. **Depression.** All reports of depression occurred in controlled trials. The distribution of subjects reporting depression, by sex and dose, was as follows:

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	Male	Female
20 mg	1	-
15 mg	3	5
10 mg	1	1
5 mg	1	2
Totals	6	8

Five CRFS contained no comment by the investigator. One patient's (**LSH12/Weiss -**) depression cleared when study drug was discontinued. The comments included in the other eight CRFS may be summarized as follows:

Multiple life stressors	4
Prior history of depression	3
Recent Hx of Halcion dependence	1

4. **Hallucinations.** A total of 9/10 reports occurred during daytime dosing in Clin Pharm trials. In 8/10 cases, the event was associated with the hypnagogic state; one patient had cocaine metabolites in his blood; no comment was recorded for the 10th subject.

5. **Miscellaneous.** Following is a summary of all other complaints, grouped by dose.

>20 mg - restless, agitated, inappropriate speech

20 mg - hyperactive, talkative/playful, spacey, seeing things floating, feeling of detachment, eyes glazed, behavioral change (quiet, withdrawn), alternately sluggish and hyperactive, crying

15 mg - decreased inhibition, forgetfulness, bad mood, hysteria

10 mg - hyperactive, hyper sensation, feeling spacey, argumentative, agitation, panic attack, crying

5 mg - way-out thoughts, agitated, argumentative

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19-908 / Ambien

Discussion Virtually all reports of amnesia / memory loss, depression, and hallucinations occurring at recommended doses appear to be explainable in terms of the patient's life situation, rather than as possible pharmacologic effects of Ambien®. Events were usually mild/moderate in intensity, lasted no more than a few hours, and left no residuals.

Recommendations Labelling should reflect the single instances of memory impairment and depression which were reported at 10 mg and were not otherwise explainable.

David M Collins, MD

cc: IND
HFD-120
HFD-120/Laughren
/Mille
/Collins
ft/dmc/November 25, 1992

Div File
N19-908

Review and evaluation of clinical data

NOV - 2 1992

NDA	19-908
Sponsor	Lorex Pharmaceuticals Skokie, Illinois
Drug	Ambien (zolpidem tartrate)
Drug class	1-C
Proposed indications	Sedative-hypnotic
Material reviewed	Responses to 4.21.92 Approvable letter (43 vols)
Date of correspondence	July 30, 1992
Date received	Aug 04, 1992
Safety review date	Nov 02, 1992
Related INDs	-

Background The Agency's 4.21.92 Approvable letter contained 11 requests for clarification or additional information. Sponsor's replies are itemized in accordance with these requests, as is the following review.

1. Re-analysis of efficacy data for LSH .

Study **LSH** was a randomized, double-blind, four-sites sleep laboratory study comparing the hypnotic efficacy of 10 and 15 mg zolpidem with placebo via a parallel groups design. Treatment consisted of a four-day placebo screening period, a one-week placebo baseline period, five weeks of nightly treatment, double-blind, and a three-day post-treatment placebo phase to assess

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discontinuation effects. Analyses summarized in the original report included analyses for each treatment week of the actual values (unadjusted for baseline) and of the change from baseline for the primary efficacy variables (latency to persistent sleep and sleep efficiency).

At the Agency's request, the sponsor carried out analyses of change from baseline for three secondary variables (number of awakenings as assessed from the PSG record, subjective sleep latency, and subjective number of awakenings), as well as analyses of covariance for all five variables, with the baseline value as covariate.

Overall, the change from baseline ANOVA analyses yielded the same pattern of statistical significance found in the original analyses of unadjusted values. ANCOVA analysis resulted in some differences in the pattern of satistical significance only with respect to the secondary variables. While these differences tended to indicate greater efficacy for the 15 mg dose compared with the 10 mg dose, the sponsor notes that these findings were not replicated in the other four studies examining 10 and 15 mg concurrently, and that the higher dose is associated with markedly higher AE rates.

Results reported in this submission are also being reviewed by Division of Biometrics (HFD-710).

2. Labelling.

Sponsor submits new labelling, incorporating many of the changes recommended by the Agency and providing alternative language for certain sections where data specific to zolpidem are available. Three versions are submitted, and are included in Volume 1: a portrait version (Section A); a side-by-side comparison of the Agency's version with sponsor's response (Section B); and an annotated version of sponsor's revision (Section C). All three have been prepared using WordPerfect 5.1; diskettes are available on request.

3. Patient Package Insert.

Sponsor agrees to the inclusion of a PPI; their draft, modified slightly from the Agency's proposal, is included in the above-described labelling.

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4. Safety Update.

Volume 28 of the present submission contains sponsor's report; volumes 29-41 contain raw data relevant to the safety update. The update includes all clinical data from the time of the original database cutoff, June, 1988, through June 13, 1991; data on 3,467 patients are included; the US (Lorex) and non-US databases are discussed separately.

There were no deaths associated with the use of zolpidem. No severe, unusual, or unexpected AEs were reported at any dose. Doses of 5-90 mg were reported.

Treatment emergent AEs occurred in 744/1701 (43.7%) of zolpidem patients in all Lorex studies at all doses; in controlled studies, overall incidence was 336/1072 (31.3%). Incidence of AEs among placebo patients was 167/634 (26.3%). Principal AEs (incidence ≥1%) were as follows:

	All studies	Controlled sleep studies	
	All doses of ZPD	ZPD ≤10 mg	Placebo
	N=1701	N=837	N=634
Drowsiness	152 (9%)	24 (3%)	10 (2%)
Dizziness	95 (6%)	16 (2%)	3 (1%)
Diarrhea	25 (2%)	13 (2%)	4 (1%)
Lightheadedness	81 (5%)	8 (1%)	2 (<.5%)
Pharyngitis	23 (1%)	8 (1%)	2 (<.5%)
Sinusitis	22 (1%)	8 (1%)	4 (1%)

These incidences are comparable to those reported in the original NDA. In general, AEs increased with the 15 and 20 mg doses.

There was no evidence of zolpidem-related abnormalities in clinical laboratory tests, vital signs, or ECGs.

Results in the non-US studies were comparable.

5. World Literature Update.

Vol 43 of the present submission contains an updated listing of papers dealing with the safety of zolpidem. Systematic review fails to identify new findings affecting current conclusions regarding zolpidem's safety.

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6. Foreign regulatory update/labelling.

Sponsor submits an updated listing of countries where zolpidem is marketed; identifies tradenames specific to each country; and provides approval and launch dates, as well as foreign language package inserts with English-language translations.

Status of zolpidem in the UK, Sweden, and Norway is discussed at Vol 1, Tab E: approval was refused in the UK; applications in the other two countries were withdrawn prior to expected denial. In all three countries, failure to include the US data was the principal reason for negative action on the applications. Sponsor is planning to include the US data in re-submissions scheduled for later this year.

7. Biopharmaceutics.

Sponsor has carried out a pharmacokinetic/pharmacodynamic study of single- and repeat-dose zolpidem in patients with renal failure undergoing hemodialysis; results are reported in Vol 27. This study is under separate review by Division of Biopharmaceutics; results appear to confirm that dosage adjustment in this patient population is not required.

Also included under this heading are data on test methods and specifications for dissolution of Ambien tablets; these data are also under review by HFD-420.

8. Manufacturing update.

Data submitted under this heading include:

a) updates on new packaging components,
b) description of revised tablet manufacturing process,
c) revisions to the DMF , and
d) stability data for drug product and proposed packaging.

These data are under separate review.

9. Pharmacology.

Current labelling includes reference to liposarcomas found in rat carcinogenicity studies. Sponsor is reviewing additional data regarding historical controls of the species used

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in these studies. Preliminary findings suggest that the numbers found in the zolpidem studies are consistent with those in the literature.

10. Final Printed Labelling.

Submission of FPL is deferred pending completion of Agency review of the present submission.

11. Advertising copy.

Also deferred.

Discussion Sponsor has been responsive to all requests for additional information. No new safety or efficacy concerns emerge from a review of the data submitted. Revised labelling conforms to Agency recommendations. Concurrence of Biometrics and Biopharmaceutics is needed for items #1 and #7, as noted above. Review of Pharmacology and Manufacturing sections is pending.

Recommendations Sponsor to sub + PL and initial advertising.

David M Collins, MD

cc:IND
HFD-120
HFD-120/Laughren
/Mille
/Collins
ft/dmc/August 19, 1992

HFD-120 / Div File

M E M O R A N D U M

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

DATE: November 19, 1991

FROM: Thomas P. Laughren, M.D. Thomas P. Laughren
Group Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Supervisory Overview for NDA 19-908 Ambien (zolpidem)

TO: File NDA 19-908
[Note: This overview should be filed with the 1-26-89 original submission.]

Table of Contents

1.0 BACKGROUND

Zolpidem is a member of the imidazopyridine class that is being proposed for use as an hypnotic at a dose of 5 to 10 mg (5 and 10 mg film-coated tablets). The sponsor has proposed that zolpidem is useful for the treatment of transient, short-term, and chronic insomnia. Although zolpidem is not a benzodiazepine, it apparently acts through the benzodiazepine receptor. Zolpidem is selective for the omega$_1$ (benzodiazepine$_1$) receptor subtype, and the sponsor has proposed that this selectivity confers a more selective pharmacological profile. They argue that zolpidem (1) has a rapid onset of action, (2) induces a sleep that is 'natural' in the sense that it does not substantially alter stage 3/4 and REM sleep, (3) is not associated with rebound insomnia, tolerance to hypnotic effects, or a withdrawal syndrome, and (4) does not affect respiratory drive in normal volunteers. The proposed name for this product is 'Ambien.'

Zolpidem was originally developed by this development program included clinical trials in Europe and South America. Subsequently, clinical trials were conducted in the US by Lorex, under IND Thus, the clinical database includes data from both the and the Lorex programs.

The zolpidem NDA was submitted 1-26-89 and was received 1-30-89. A critical problem for the NDA that was recognized early in the review process was the fact that the synthesis for the to-be-marketed product was changed from that used for the product studied in the clinical trials, resulting in new impurities. This change necessitated additional bioequivalence trials as well as additional nonclinical toxicity studies. The results from the additional bioequivalence trials were submitted 6-28-91 and the results from the additional toxicity studies were submitted 4-1-91. Revised draft labeling was submitted 5-17-91 and a draft SBA was submitted 6-28-91.

Zolpidem is currently marketed in France, Belgium, Italy, Denmark, and Luxembourg; it is approved, but not marketed, in Greece, the Netherlands, Switzerland and Germany.

We have not taken zolpidem to the Psychopharmacological Drugs Advisory Committee, and it has not been the subject of an 'NDA Day.'

2.0 CHEMISTRY

Ambien (zolpidem) is being proposed for marketing as 5 and 10 mg film coated tablets. As of this date, there are no chemistry issues that would preclude approvability. Final approval, however, is contingent on the satisfactory completion of plant inspections of two French facilities (for drug substance) and one Puerto Rico facility (drug product). All three inspections are scheduled and should be completed in the near future.

There is one additional issue that I believe should be resolved before final approval. We have recently required the manufacturers of all currently marketed benzodiazepine hypnotics to provide for unit-of-use packaging for outpatient distribution of hypnotics. This packaging would provide for no more than 10 doses of the hypnotic per package, and it would contain the Patient Package Insert (PPI) as part of the packaging. It is my recommendation that we require Lorex to provide for the packaging of Ambien in this manner before we finally approve this product.

The chemistry reviewer has recommended no changes in the sponsor's proposed labeling, and has suggested minor changes in the chemistry section of the sponsor's proposed SBA. I have provided comments in the "How Supplied' section of labeling regarding a requirement for unit-of-use packaging, and we have modified the chemistry section of the SBA as suggested.

3.0 PHARMACOLOGY

Two pharmacology issues emerged during the course of the review of this NDA, one involving a question of the toxicity of impurities, and the second involving the occurrence of renal liposarcomas in the rat carcinogenicity study.

The impurity question arose because of a change in the synthesis methods for zolpidem during the course of the review. In an 8-15-90 letter, we asked the sponsor to conduct an additional 1 month oral toxicity study in the rat and to repeat the mutagenicity screen. The data from these additional studies were submitted 4-1-91, and they satisfactorily resolved this question.

The carcinogenicity question arose because of a finding of renal liposarcomas in 1 MDM (2%) and 3 HDM (6%) in the two year rat study, with none in the LDM or CM groups. However, a survey of historical controls revealed a background rate of 0-4%. In addition, the 1 year rat study was negative and the mutagenicity screens were all negative. Consequently, the pharmacology group concluded that this finding was probably not related to zolpidem. Nevertheless, the finding will be noted in labeling, it will be discussed at the Carcinogenicity Committee before final approval, and the sponsor will be asked to repeat the rat carcinogenicity study post-approval.

The pharmacology reviewer has recommended changes in labeling, and these have been made. Dr. Wilk recommended one minor change in the draft SBA, and this change has also been made.

4.0 BIOPHARMACEUTICS

Zolpidem is fairly rapidly absorbed, with a Tmax of 1-2 hours. It is also rapidly cleared, with an elimination $T_{1/2}$ of 2-3 hours. There is no accumulation of zolpidem during dosing. The $T_{1/2}$ is increased by

roughly 50% in the elderly, and substantially increased in patients with hepatic cirrhosis. Zolpidem is 92% protein bound and has no active metabolites. There is a slight decrease in peak concentration when it is given with meals, but the change is of doubtful clinical significance.

Single dose interaction studies showed no prominent PK interactions with haloperidol, imipramine, chlorpromazine, cimetidine, ranitidine, digoxin, or warfarin. There were additive CNS depressant effects with imipramine and chlorpromazine, but none were apparent with alcohol.

Early bioequivalence studies raised the question of lack of equivalence between the clinically studied capsule and the to-be-marketed tablet. However, later studies demonstrated equivalence.

The Division of Biopharmaceutics concluded that the sponsor has fulfilled their requirements for this NDA. They have recommended dissolution specifications and a Phase IV tablet study in patients with renal compromise to supplement the i.v. study.

Extensive changes have been made to the pharmacokinetics and drug interactions subsections of labeling, and minor changes have been made in the sponsor's draft SBA.

Doc ZOLPMEM.1

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Efficacy Data

Forty-one efficacy trials were referred to in the NDA in support of the efficacy claim for zolpidem, including 8 conducted by Lorex in the US and Canada and 33 by
in Europe and South America. Twenty-seven of the trials were controlled and 14 were uncontrolled. However, because of (1) insufficient data for review of most of the trials, and/or (2) substantial flaws in the design or conduct of studies, this summary will focus on a small subset of these trials. Three definitive Lorex trials will be described in detail under 5.1.2, including one in insomnia and two in insomnia; 4 supportive trials will be summarized, generally more briefly, under 5.1.3.

Under subsections 5.1.2 and 5.1.3 to follow, only results pertaining to efficacy will be presented. Other findings pertaining to next day residual effects and rebound insomnia will be presented under section 5.2 (Safety Data).

5.1.2 Studies Providing Primary Evidence of Effectiveness

5.1.2.1 LSH "Dose-Response Efficacy Study of Zolpidem in Subjects with Insomnia"

5.1.2.1.1 Objectives

The objectives of this trial were to (1) evaluate the hypnotic efficacy of zolpidem 7.5 and 10.0 mg in insomnia, (2) explore for a dose/response efficacy relationship in the broader range of zolpidem mg, (3) explore the tolerability of zolpidem in this population, and (4) explore the next day residual effects of zolpidem in this population.

5.1.2.1.2 Design

This was a double-blind, randomized, parallel group sleep laboratory study comparing several fixed zolpidem doses with placebo in subjects with insomnia. Two centers contributed subjects for this trial: Roth; Vogel. Subjects were normal with respect to sleep function at entry, and the model for insomnia was the 'first night effect,' i.e., the impaired sleep function seen on the first night in a sleep laboratory. There were 5 zolpidem groups (5.0, 7.5, 10.0, 15.0, and 20.0 mg) and a placebo group. The randomization was unbalanced to favor the groups for which definitive analyses were planned, i.e., 7.5 mg, 10.0 mg, and placebo. This was a single night study with medication administered 30 minutes before a pre-established bedtime. Efficacy assessments and residual effects assessments included (1) continuous polysomnographic (PSG) recording during the 8 hours scheduled time in bed, (2)

questionnaires the next morning and later that day (mail-in), (3) Digit Symbol Subscitution Test (DSST) and the Symbol Copying Test (SCT) the next morning.

This summary will focus on three primary efficacy measures obtained from PSG recording: (1) sleep efficiency (total sleep time/time in bed), (2) latency to persistent sleep (time from the beginning of the recording to the onset of the first 10 minutes of consecutive sleep), and (3) number of awakenings. Three of 10 items from the morning questionnaire were selected as secondary efficacy measures: (1) subjective sleep latency, (2) subjective total sleep time, and (3) sleep quality.

5.1.2.1.3 Conduct

Of 595 subjects screened for this study, 462 were randomized to treatment. These subjects were distributed across centers and treatment groups as follows:

	Zolpidem (mg)					
Center	5.0	7.5	10.0	15.0	20.0	Pbo
Roth	27	52	52	26	26	52
Vogel	25	50	52	25	25	50
Total	52	102	104	51	51	102

One Roth subject did not take the study medication, and two Roth subjects did not complete the required 480 minutes in bed. Consequently, the intent-to-treat sample consisted of 459 subjects.

Of the 462 subjects randomized, the demographic characteristics were as follows: the male/female ratio was 79:21; mean age = 31 (range
83% white. Comparisons of treatment groups on demographic characteristics revealed no statistically significant differences in gender, age, race, weight, or height.

5.1.2.1.4 Outcome

Primary Efficacy Measures: All efficacy analyses were conducted with the intent-to-treat sample. The primary analysis model used was analysis of variance (ANOVA) across all 6 treatment groups for each variable, with testing for treatment by investigator interaction, and Kruskal-Wallis non-parametric analysis for confirmation. Logarithmically transformed data were analyzed for two variables, i.e., sleep efficiency and sleep latency. Pairwise comparisons with placebo were done only for the 7.5 and 10.0 mg groups. Linear regression analysis was done utilizing data from all dose groups for exploring a dose/effect relationship for each variable. The following table provides mean scores for each primary efficacy variable (for the 7.5 mg, the 10.0 mg, and the placebo groups), the p-value for the overall treatment comparison, and an indication of any significant pariwise comparisons of the 7.5 and 10.0 mg groups with placebo.

LSH
Primary Efficacy Measures

Variable	Placebo (N=101)	7.5 mg (N=102)	10.0 mg (N=103)	p-value
Sleep Latency (min)	27.1	17.0*	17.4*	0.003
Sleep Efficiency (%)	87.8	91.7*	91.8*	<0.001
Number of Awakenings	6.7	5.0*	5.3*	0.024

*:Significantly different from placebo, p<0.05, 2-sided

The regression analyses for dose/response exploration were statistically significant for all of the above variables. The relationships were quadratic in form for sleep latency and sleep efficiency, and linear for number of awakenings.

Secondary Efficacy Measures: The following table provides the means for selected secondary efficacy variables (for the 7.5 and 10.0 mg groups and placebo), the p-value for the overall treatment comparison, and an indication of any significant pairwise comparisons with placebo.

LSH
Secondary Efficacy Measures

Efficacy Measures	Placebo (N=101)	7.5 mg (N=102)	10.0 mg (N=103)	p-value
Subjective Sleep Latency (min)	29	19*	18*	<0.001
Subjective Sleep Duration (hrs)	7.1	7.3	7.2	0.263
Quality of Sleep[a]	2.7	2.2*	2.2*	<0.001

*: Significantly different from placebo, p<0.05, 2-sided
[a]: Scale (1=excellent, 2=good, 3=fair, 4=poor)

5.1.2.1.5 Conclusions

This study demonstrated the hypnotic efficacy of the 7.5 and 10.0 mg zolpidem doses in a insomnia model.

5.1.2.2 LSH "Zolpidem in Insomniacs"

5.1.2.2.1 Objectives

The objectives of this trial were to (1) evaluate the hypnotic efficacy of zolpidem at doses of 10 and 15 mg in patients with insomnia, and to (2) assess patients for withdrawal effects after discontinuing zolpidem.

5.1.2.2.2 Design

This was a double-blind, parallel group study of two fixed doses of zolpidem and placebo in outpatients with insomnia. Four centers contributed patients to this trial: Roth; Scharf; Vogel; Walsh. Patients

were randomized to zolpidem 10 mg, zolpidem 15 mg, or placebo. Study subjects were outpatients who were in good health other than having insomnia defined as having all of the following complaints for a period of at least 3 months: (1) sleep duration between 4 and 6 hours, (2) sleep latency of more than 30 minutes, and (3) daytime complaints associated with poor sleep. In addition, during at least 2 of 3 sleep laboratory screening nights, subjects were to have (1) a total sleep time of 4-7 hours, and (2) a sleep latency of at least 20 minutes.

Following 1 night of adaptation and 3 nights of screening in a sleep laboratory, subjects received (1) placebo for 7 nights of a single-blind run-in phase, (2) assigned treatment (zolpidem 10 mg, zolpidem 15 mg, or placebo) for 35 nights of the double-blind phase, and (3) placebo for 3 nights of a single-blind discontinuation phase. During the first two nights of each week, patients were evaluated in the sleep laboratory, as well as for the three nights following discontinuation. Patients were to take their medication 30 minutes before their usual time of falling asleep.

The primary efficacy and residual effects assessments included (1) continuous polysomnographic (PSG) recordings during the scheduled time in bed on the sleep laboratory nights, (2) a questionnaire on the mornings following the PSG recordings, and (3) psychomotor performance tests (DSST and DSCT) on the mornings following the PSG recordings. The primary hypnotic efficacy variables obtained from the PSG recordings were (1) latency to persistent sleep, (2) sleep efficiency (total sleep time/time in bed, (3) number of awakenings. The secondary efficacy measures obtained from the morning questionnaires included subjective responses to 4 of the 10 questions: (1) sleep latency, (2) number of awakenings, (3) total duration of sleep, and (4) sleep quality.

5.1.2.2.3 Conduct

Of 178 patients screened, 75 were randomized to treatment; 67 of the randomized patients completed the trial. These patients were distributed among treatment groups as follows:

	Treatment Group			
	Placebo	10 mg	15 mg	Total
Randomized	24	26	25	75
Completed				
Number (Percent)	23(96%)	22(85%)	22(88%)	67(89%)

Post-randomization efficacy assessments were available for all randomized patients. Thus, the sample randomized was identical to the intent-to-treat sample utilized in the efficacy analysis.

The mean age of subjects in the intent-to-treat sample was 38 years (range: The male:female ratio was 36:64, and 73% of subjects were white. Mean height was 171 cm and mean weight was 77 kg. There were no statistically significant differences among treatment groups on any of these demographic variables. A comparison of treatment groups on 20

hypnotic efficacy and residual effects variables revealed only one statistically significant difference, i.e., the 10 mg group had higher effficiency (85%) than either the placebo (81%) or the 15 mg group (81%).

5.1.2.2.4 Outcome

All efficacy analyses were conducted with the intent-to-treat sample. This summary will present the results of last-observation-carried-forward (LOCF) analyses in which scores were carried forward to weeks 2 through 6, corresponding to treatment weeks 1 through 5. Means were calculated for the two weekly values of each variable prior to analysis. Analyses were done on unadjusted outcome measures, except for latency and sleep efficiency (PSG), for which change from baseline analyses were also performed. The primary analysis model was analysis of variance (ANOVA), with factors for treatment, center, and treatment-by-center interaction. Pairwise comparisons with placebo were tested whenever the overall test was significant. Logarithmically transformed data were analyzed for two variables, i.e., sleep latency and sleep efficiency (PSG).

Primary Efficacy Measures: The following table provides the mean scores for each primary efficacy variable (by treatment group and by treatment week), the p-value for the overall treatment comparison, and an indication of any significant pairwise comparisons with placebo.

LSH
Primary Efficacy Measures

Variable	Week	Placebo	10 mg	15 mg	p-value
Sleep Latency (min)	BL	49.9	35.8	47.0	0.250
	2	44.7	22.9*	21.6*	0.003
	3	51.1	24.4*	26.5*	0.023
	4	56.2	20.3*	21.6*	0.001
	5	43.8	23.5*	29.3*	0.033
	6	48.0	25.8	28.1*	0.029
Sleep Efficiency (%)	BL	80.8	85.3*	80.6	0.047
	2	81.6	88.1*	88.1*	0.022
	3	80.3	87.9*	88.0*	0.004
	4	81.8	88.1*	89.1*	0.028
	5	83.2	89.3*	88.0*	0.007
	6	80.7	87.9	87.3*	0.027
Number of Awakenings	BL	7.0	8.2	8.6	0.905
	2	7.0	6.2	7.5	0.309
	3	5.6	6.9	8.3	0.223
	4	6.8	6.0	7.7	0.511
	5	6.3	6.7	8.6	0.363
	6	6.7	6.7	7.7	0.649

*: Significantly different from placebo, $p<0.05$ (2-sided)

Secondary Efficacy Measures: The following table provides the mean scores for each secondary efficacy variable (by treatment group and by treatment week), the p-value for the overall treatment comparison, and an indication of any significant pairwise comparisons with placebo.

LSH
Secondary Efficacy Measures

Variable	Week	Placebo	10 mg	15 mg	p-value
Subjective Sleep Latency (min)	BL	70.4	57.0	61.0	0.955
	2	61.1	43.5	33.5*	0.032
	3	63.2	34.9	30.7*	0.014
	4	72.7	37.6*	32.3*	0.001
	5	69.2	37.5*	35.2*	0.003
	6	56.6	38.4	31.7*	0.004
Subjective Total Sleep Time (min)	BL	331	331	332	0.964
	2	355	361	394	0.131
	3	351	362	384	0.345
	4	340	356	397*	0.036
	5	325	358*	389*	0.001
	6	356	369	394	0.093
Subjective Number of Awakenings	BL	2.8	3.8	3.7	0.421
	2	2.4	2.8	1.6*	0.002
	3	2.4	2.7	2.5	0.948
	4	2.1	2.8	1.9	0.167
	5	2.7	3.1	2.5	0.383
	6	2.5	2.7	2.2	0.436
Sleep Quality[a]	BL	2.7	2.8	2.9	0.272
	2	2.4	2.7	2.2	0.050
	3	2.8	2.5	2.4	0.222
	4	2.7	2.7	2.2	0.084
	5	2.7	2.6	2.4*	0.032
	6	2.6	2.5	2.5	0.536

*: Significantly different from placebo, $p<0.05$ (2 sided)
[a]: Scale (1=excellent, 2=good, 3=fair, 4=poor)

5.1.2.2.5 Conclusions

This study demonstrated the hypnotic efficacy of zolpidem at doses of 10 and 15 mg in patients with insomnia. The effects on sleep latency and sleep efficiency persisted for all 5 treatment weeks for the 15 mg dose, and for the first 4 weeks for the 10 mg dose. The subjective assessments of sleep latency also favored active drug over placebo, but the other subjective measures of hypnotic effect were less consistently positive.

5.1.2.3 LSH "Zolpidem in Outpatients with Insomnia"

5.1.2.3.1 Objectives

The objectives of this trial were to (1) evaluate the hypnotic efficacy of zolpidem at doses of 10 and 15 mg in patients with insomnia, and to (2) assess patients for withdrawal effects after discontinuing zolpidem.

5.1.2.3.2 Design

This was a double-blind, parallel group study of two dose of zolpidem (10 and 15 mg) and placebo in patients with insomnia. Six centers contributed patients to this trial: Docherty; Fillingim; Lahmeyer; Cohn; Kann; Leppik. Patients were randomized to zolpidem 10 mg, zolpidem 15 mg, or placebo in a ratio of 4:4:5. Study subjects were outpatients who were in good health other than having insomnia defined as having all of the following complaints for a period of at least 3 months: (1) sleep duration between 4 and 6 hours, (2) sleep latency of more than 30 minutes, and (3) daytime complaints associated with poor sleep.

Following screening, subjects received (1) placebo for 3 nights of a single-blind run-in phase, (2) assigned treatment (zolpidem 10 mg, zolpidem 15 mg, or placebo) for 21 nights of the double-blind phase, and (3) placebo for 4 nights of a single-blind discontinuation phase. Patients were to take their medication 30 minutes before their usual time of falling asleep.

Patients were seen weekly during this approximately 6 week trial. Hypnotic efficacy was assessed with a Morning Questionnaire completed on days 1,2,3, and 7 of each week. The critical efficacy variables included patients' subjective assessments of the following: sleep latency; total sleep time; number of awakenings; sleep quality.

5.1.2.3.3 Conduct

Of 178 patients screened, 145 were randomized to treatment; 118 of the randomized patients completed the trial. These patients were distributed among treatment groups as follows:

	Treatment Group			
	Placebo	10 mg	15 mg	Total
Randomized	54	45	46	145
Completed				
Number (Percent)	44(81%)	37(82%)	37(80%)	118(81%)

Post-randomization efficacy assessments were available for 140 randomized patients; 5 patients discontinued during the placebo run-in. Thus, the intent-to-treat sample consisted of 140 patients.

The mean age of subjects in the randomized sample was 45 years (range:). The male:female ratio was 44:56, and 92% of subjects were white.

Mean height was 171 cm and mean weight was 75 kg. There were no statistically significant differences among treatment groups on any of these demographic variables, or on any of the baseline measures of sleep function.

5.1.2.3.4 Outcome

The following efficacy analyses were conducted with the intent-to-treat sample. This summary will present the results of last-observation-carried-forward (LOCF) analyses in which scores were carried forward to weeks 2, 3, 4, and 5, corresponding to treatment days 7, 14, 21, and 28. Data from the Docherty and Kann centers were combined to create a new center roughly equal in size to the other centers. The proportional hazards model was used for analyzing the subjective sleep latency data because there was some censoring of data for this variable, i.e., patients reported they had not fallen asleep. This model was stratified by investigator to control for investigator effect. The statistic was used to test pairwise comparisons with placebo whenever the overall test was significant. All other efficacy variables were analyzed using analysis of variance, with effects for treatment, center, and treatment-by-center interaction.

Primary Efficacy Measures: The following table provides the mean scores for each primary efficacy variable (by treatment group and by treatment week), the p-value for the overall treatment comparison, and an indication of any significant pairwise comparisons with placebo.

LSH
Primary Efficacy Measures

Variable	Week	Placebo	10 mg	15 mg	p-value
Subjective Sleep Latency (min)	BL	58.2	65.1	75.9	0.325
	2	61.0	34.5*	38.1*	0.004
	3	49.7	34.0*	33.1*	0.026
	4	60.7	32.0*	33.4*	0.005
	5	42.8	26.8*	33.0	0.039
Subjective Total Sleep Time (min)	BL	315	316	308	0.975
	2	331	377*	378*	0.005
	3	348	373	384	0.060
	4	344	375	375	0.077
	5	360	390	385	0.229
Subjective Number of Awakenings	BL	2.6	2.5	2.7	0.916
	2	2.1	1.2*	1.5*	0.001
	3	1.9	1.4	1.2*	0.032
	4	1.7	1.2	1.3	0.122
	5	1.7	1.4	1.2	0.172
Sleep Quality[a]	BL	3.0	2.9	3.2	0.204
	2	3.0	2.3*	2.4*	<0.001
	3	2.8	2.5	2.4*	0.035
	4	2.7	2.3	2.4	0.076
	5	2.6	2.4	2.4	0.479

*: Significantly different from placebo, $p<0.05$
[a]: Scale Values (1=excellent, 2=good, 3=fair, 4=poor)

Assessment of Tolerance:

The sponsor's approach to assessing tolerance was to compare changes from baseline on sleep latency and total sleep time after one week and after 4 weeks, within each treatment group. While they were able to show that there was no worsening of function on these variables in any of the treatment groups, there was no statistically significant difference between active drug groups and placebo beyond 2 weeks of treatment, except for sleep latency. This failure to find a difference late in treatment most likely resulted from greater improvement on the remaining three efficacy variables in the placebo group than in the active drug groups during the third and fourth weeks of treatment. While such a finding does not argue against a lack of tolerance to zolpidem over 4 weeks of treatment, it does preclude making any inference about the persistence of

an effect on total sleep time, number of awakenings, and sleep quality.

5.1.2.3.5 Conclusions

This study demonstrated the hypnotic efficacy of zolpidem at doses of 10 and 15 mg in patients with insomnia. The effect on sleep latency persisted for all 4 weeks for the 10 mg dose, and for 3 weeks for the 15 mg does. However, the effects on total sleep time, number of awakenings and sleep quality were present for only the first treatment week for the 10 mg dose. Similarly, the effect on total sleep time was present for only the first treatment week at the 15 mg dose, but was present for 2 weeks for number of awakenings and sleep quality in this higher dose group. No conclusions can be drawn about tolerance to the effects on total sleep time, number of awakenings and sleep quality, since patients in the placebo group improved on these variables over the course of the study, and thus, there was no group with which a fair comparison to the active drug groups could be made.

5.1.3 Other Studies Pertinent to Efficacy

5.1.3.1 LSH "Dose-Response Study of the Effect of Zolpidem on Insomnia Produced by 3-Hour Phase Advance"

5.1.3.1.1 Objectives

The objectives of this trial were to (1) evaluate the hypnotic efficacy of zolpidem 5, 10, 15, and 20 mg in insomnia, and to (2) explore the next day residual effects of zolpidem in this population.

5.1.3.1.2 Design

This was a single center (Walsh), double-blind, randomized sleep laboratory study comparing several fixed doses of zolpidem with placebo in subjects experiencing sleep difficulty resulting from a 3-hour phase advance of their bedtime. It consisted of two independent 3-period crossovers as follows: I (placebo, zolpidem 10 mg and 20 mg); II (placebo, zolpidem 5 mg and 15 mg). Subjects were normal with respect to sleep function at entry. Each study period consisted of two nights in the sleep laboratory. On night 1, each subject received placebo 30 minutes before his/her usual bedtime. On night 2, the bedtime and study drug (zolpidem or placebo) were advanced 3 hours compared to night 1. Efficacy and residual effects assessments included (1) continuous polysomnographic (PSG) recording during the 8 hours scheduled time in bed, (2) a questionnaire the next morning, (3) psychomotor performance tests the next morning (DSST and DSCT), and (4) sleep latency tests at 1 and 3 hours after waking.

This summary will focus on three primary efficacy measures obtained from PSG recording: (1) sleep efficiency (total sleep time/time in bed), (2) latency to persistent sleep (time from the beginning of the recording to the onset of the first 10 minutes of consecutive sleep), and (3) number of awakenings. Three of 10 items from the morning questionnaire were

selected as secondary efficacy measures: (1) subjective sleep latency, (2) subjective total sleep time, and (3) sleep quality.

5.1.3.1.3 Conduct

Of 53 subjects screened for this study, 34 were randomized to treatment. However, 3 of the randomized subjects withdrew after the first placebo night of period 1, leaving only 31 who completed the 3-period treatment phase. Two additional subjects from crossover I were excluded from the analysis due to serious protocol violations: one subject had a sleep latency greater than 60 minutes, and the other had a 2-hour change in bedtime after period 1. Consequently, the samples for data analysis were N=13 for crossover I and N=16 for crossover II.

Of the 31 subjects who completed the study, the demographic characteristics were as follows: the male/female ratio was 29:2; mean age = 24 (range: ; 87% white.

5.1.3.1.4 Outcome

The primary analysis model used was analysis of variance (ANOVA), including effects for sequence, subject within sequence, period, and treatment. Logarithmically transformed data were analyzed for sleep efficiency and sleep latency. When there were significant differences ($p<0.05$) among treatments, pairwise comparisons of placebo with the active drug groups were provided. Because of wider variability in crossover I than crossover II, the data were not pooled for analysis, and the results from the independent crossovers are presented separately.

Primary Efficacy Measures: The following tables provide the mean scores for each primary efficacy variable by treatment period, the p-value for the overall treatment comparison, and an indication of any significant pairwise comparisons with placebo.

LSH

Primary Efficacy Measures-Crossover I (N=13)

		Zolpidem		
Variable	Placebo	10 mg	20 mg	p-value
Sleep Latency (min)	25	17	26	0.834
Sleep Efficiency (%)	84	93	89	0.129
Number of Awakenings	4	5	5	0.431

*:Significantly different from placebo, $p<0.05$, 2-sided

LSH
Primary Efficacy Measures-Crossover II (N=16)

Variable	Placebo	Zolpidem 5 mg	Zolpidem 15 mg	p-value
Sleep Latency (min)	13	10	6	0.152
Sleep Efficiency (%)	86	93*	94*	0.034
Number of Awakenings	6	5	5	0.712

*:Significantly different from placebo, p<0.05, 2-sided

Secondary Efficacy Measures: The following tables provide the mean scores for each secondary efficacy variable by treatment period, the p-value for the overall treatment comparison, and an indication of any significant pairwise comparisons with placebo.

LSH
Secondary Efficacy Measures-Crossover I (N=13)

Variable	Placebo	Zolpidem 10 mg	Zolpidem 20 mg	p-value
Subjective Sleep Latency (min)	27	20	21	0.472
Subjective Sleep Duration (min)	415	456*	443*	0.013
Quality of Sleep[a]	2.7	2.3	2.4	0.151

*:Significantly different from placebo, p<0.05, 2-sided
[a]: Scale (1=excellent, 2=good, 3=fair, 4=poor)

LSH
Secondary Efficacy Measures-Crossover II (N=16)

Variable	Placebo	Zolpidem 5 mg	Zolpidem 15 mg	p-value
Subjective Sleep Latency (min)	27	16	15	0.055
Subjective Sleep Duration (min)	432	448	464*	0.012
Quality of Sleep[a]	2.6	2.1*	2.1*	0.033

*: Significantly different from placebo, p<0.05, 2-sided
[a]: Scale (1=excellent, 2=good, 3=fair, 4=poor)

5.1.3.1.5 Conclusions

While this study is suggestive of a hypnotic effect for zolpidem, the findings are not consistent enough to be considered a definitive source of support. The failure of this study to clearly demonstrate an hypnotic effect for zolpidem may have resulted, in part, due to the failure of the model to induce significant sleep impairment.

5.1.3.2 LSH01

This was an early dose ranging study to establish the clinical activity of zolpidem. It was a single center (Roth) sleep laboratory study utilizing a randomized, double-blind, placebo-controlled, crossover design. Five doses of zolpidem (2.5, 5.0, 7.5, 10.0, and 20.0 mg) and placebo were studied in 12 normal male volunteers. There were six 3-night PSG evaluations, with subjects receiving assigned medication on the first two nights and placebo on the third night. Morning questionnaires supplemented the PSG recordings. Both latency to persistent sleep and subjective sleep latency were statistically significantly superior to placebo for zolpidem doses of 5.0 mg and greater. While other subjective measures of sleep function (total sleep time, perceived awakenings, and sleep quality) were also statistically significantly supreior to placebo for zolpidem doses of 7.5 mg and greater, no statistically significant differences with placebo were seen for the PSG variables of sleep efficiency and number of awakenings. Thus, this study was considered only supportive of the hypnotic efficacy of zolpidem.

5.1.3.3 LSH11

This was an early dose ranging study to establish the clinical activity of zolpidem in a normal elderly population. It was a single center (Scharf) sleep laboratory study utilizing a randomized, double-blind, placebo-controlled, crossover design. There were two independent groups, one receiving zolpidem 5 and 15 mg, and placebo (N=17) and the second receiving zolpidem 10 and 20 mg, and placebo (N=18). Subjects in each group had three 3-night PSG evaluations, with subjects receiving assigned medication on the first two nights and placebo on the third night. Morning questionnaires supplemented the PSG recordings. All four zolpidem doses were statistically significantly superior to placebo for two key PSG variables, i.e., latency to persistent sleep and sleep efficiency, and for four key subjecitve sleep measures, i.e., sleep latency, total sleep time, perceived awakenings and sleep quality. Thus, this study was considered strongly supportive of the hypnotic efficacy of zolpidem.

5.1.3.4 RUTHER/IGE01

This was also an early dose ranging study to establish the clinical activity of zolpidem. It was a single center (Ruther) sleep laboratory study utilizing a randomized, double-blind, placebo-controlled, crossover design. Two doses of zolpidem (10 and 20 mg), lormetazepam 1 mg, triazolam 0.5 mg, and placebo were compared in 10 normal male volunteers. Each subject had five 2-night PSG evaluations, with placebo being administered on the first night and assigned medication on the second. The only PSG variable shown to be statistically significantly superior to placebo was latency to persistent sleep, for both zolpidem doses and for lormetazepam. This study was considered weakly supportive of the hypnotic efficacy of zolpidem.

5.1.4 Conclusions Regarding Efficacy Data

In my view, study LSH provided strong evidence for the hypnotic efficacy of zolpidem at doses of 7.5 and 10 mg in insomnia. This finding was strongly supported by one of the early pilot studies, LSH11, and less strongly by the phase advance study, LSH and by the two other pilot studies, LSH02 and Ruther/IGE01. The two trials in subjects with insomnia, LSH and LSH were also positive enough, in my view, to be considered primary evidence for the hypnotic efficacy of zolpidem in insomnia at doses of 10 and 15 mg, despite the fact that neither study was as consistently positive as one might hope for.

5.2 Safety Data

5.2.1 Clinical Data Sources

5.2.1.1 Population Exposed

The clinical database in support of this NDA came from two sources: clinical trials conducted by (1) and by (2) Lorex in the US and Canada. The data to follow approximate the clinical exposures to zolpidem from these two sources as of June, 1988. I was assured in a 2-4-91 conversation with Keith Rotenberg of Lorex that there were only 100-200 additional patients in the database since the original submission, and that none had any previously unrecognized adverse events.

The program for the hypnotic efficacy of zolpidem consisted of 81 studies: Phase 1 (47); Phase 2 (23); Phase 3 (11). A total of N=2412 subjects participated in these trials, including N=1856 who received zolpidem. Complete safety data were available for only 30 of these 81 trials, including data from N=1336 subjects who received zolpidem in these trials. Nevertheless, data for any deaths or withdrawals for adverse events were available for the remaining trials, and consequently, the total zolpidem exposed sample for which safety data were available from the hypnotic program was N=1856. In addition, conducted 13 trials of zolpidem as a premedicant, involving N=604 adult subjects and N=99 pediatric subjects exposed to zolpidem.

The Lorex program for the hypnotic efficacy of zolpidem consisted of 17 studies, including 9 clinical pharmacology trials, 6 controlled efficacy trials, and 2 uncontrolled trials. A total of N=1184 subjects participated in these trials, including N=940 who received zolpidem.

The total sample of zolpidem exposed patients/subjects for whom safety data were available is as follows:

Hypnotic	1856
Premedicant-Adult	604
Premedicant-Children	99
Lorex	
Hypnotic	940
Total	3499

While zolpidem is marketed in a number of European countries, only limited postmarketing data were available as part of this application. The original application included brief comments on overdoses in France, and a 6-28-91 amendment included a brief summary of post-marketing data from three years of European experience. The adverse event profile in this post-marketing report was consistent with that seen in the clinical trials experience.

5.2.1.2 Extent of Exposure

In the hypnotic development program, patients were exposed to zolpidem doses ranging from mg to more than mg, for durations ranging from nights to greater than month. However, the emphasis in that program was on doses of 10 and 20 mg. The following table (Table 7 from a 6-28-91 submission) provides the distribution of zolpidem patients in the hypnotic program by mean dose and duration. This is a mutually exclusive distribution in which patients are counted only once. It includes data from the 30 trials for which such data were available.

ZOLPIDEM PATIENTS BY DOSE AND DURATION - PROGRAM

	MEAN ZOLPIDEM DOSE (MG)							
DURATION	2.5	5	7.5	10	15	20	30	≥ 35
1-2 nights	0	22	0	38	0	47	24	0
3-7 nights	0	1	2	70	12	147	11	0
8-28 nights	1	68	7	203	9	243	2	0
≥ 1 month	0	1	3	71	31	286	17	7

In addition, conducted a premedicant program for zolpidem in which patients were exposed to 1-2 doses of zolpidem in doses ranging from mg. The 30 mg dose was discontinued after the first 33 subjects were exposed.

In the Lorex hypnotic development program, patients were exposed to zolpidem doses ranging from 2.5 mg to more than 40 mg, for durations ranging from nights to greater than weeks. However, the emphasis in that program was on doses of 10 and 15 mg. The following table (Table 6 from a 6-28-91 submission) provides the distribution of zolpidem patients in the Lorex hypnotic program by dose and duration. This is not a mutually exclusive distribution, i.e., patients are counted more than once.

ZOLPIDEM DOSE AND DURATION - LOREX PROGRAM

	ZOLPIDEM DOSE (MG)							
DURATION	2.5	5	7.5	10	15	20	30-40	> 40
1-2 nights	12	110	114	195	105	185	84	58
3-7 nights	0	0	0	4	25	0	0	0
1-2 weeks	0	0	0	5	21	0	0	0
3-6 weeks	0	0	0	70	100	0	0	0
> 6 weeks	0	0	0	18	147	0	0	0

5.2.1.3 Demographics

Reasonably complete demographic data were available only for 30 of the 81 trials in the hypnotic development program. Among subjects participating in those trials, the mean age was 61 years, with a range of Females outnumbered males by a ratio of approximately 2:1. Subjects in the LERS premedicant program ranged in age from and the female to male ratio was approximately 1.7.

The mean age in the Lorex hypnotic program was 35 years, with a range of In this program, males outnumbered females, with a male to female ratio of approximately 2.2. Subjects in the Lorex program were distributed by race as follows: white-80%, black-17%, other-3%.

5.2.2 Special Safety Considerations

5.2.2.1 Deaths Associated with Zolpidem Treatment

No deaths occurred in Lorex sponsored trials. There were 9 deaths reported among patients participating in trials sponsored by including 5 during treatment with zolpidem, 1 after discontinuing zolpidem treatment, 2 during treatment with placebo, and 1 during treatment with a comparative agent. All 9 patients were elderly and had concomitant medical illnesses. In none of the zolpidem-treated patients could the deaths be reasonably attributed to zolpidem treatment.

5.2.2.2 Zolpidem Overdose Experience

[Note: These comments are based on an overdose summary contained in the 6-28-91 submission.]

No overdoses were reported in the clinical trials for zolpidem. The only information available on overdose with zolpidem came from postmarketing reports from France, where zolpidem has been available since March, 1988.

These included 3 cases of accidental overdose and 51 intentional overdoses.

Two of the accidental overdoses occurred in children (3 year old, 20 mg; 13 year old, 40 mg) and one in a severely debilitated elderly male (20 mg bid for three days). Somnolence was the only symptom observed, and all three fully recovered.

Zolpidem was taken alone in 32 of the 51 intentional overdoses, at doses up to 400 mg. Symptoms were mild for most cases, but there was one case each of cardiovascular and respiratory compromise, and two cases of reactive coma. All patients fully recovered.

All 19 cases involving poly-intoxication were symptomatic, including 11 cases of coma and two cases of cardiorespiratory depression. All but two of these cases recovered. One death occurred in a patient who overdosed with vinylbarbital 2000 mg, meprobamate 4000 mg, and zolpidem 600 mg. A second patient died following an overdose with methaqualone 400 mg, clorazepate 400 mg, zolpidem 300 mg, and an unknown amount of alcohol. The role of zolpidem in these two deaths cannot be determined.

5.2.2.3 Significant/Potentially Significant Events Considered Possibly/Probably/Definitely Drug Related

The important drug-related adverse events for zolpidem are those that are common to the group of sedative/hypnotic drugs, i.e., drowsiness, dizziness, lightheadedness, lethargy, 'drugged feeling,' and amnesia.

5.2.2.4 Other Significant Events Considered Not Drug Related

In addition to the deaths noted above as not considered causally related to zolpidem use, there were a number of other patients in the and Lorex programs who discontinued for significant adverse medical events that were, upon review, considered not causally related to zolpidem use. These included the following events among patients: supraventricular tachycardia, myocardial infarction, renal colic, diarrhea and weight loss, cerebral hemorrhage. The following events were considered to be not causally related to zolpidem use among patients discontinuing from the Lorex program: chest pain, elevated AST/ALT, flu symptoms, pneumonia, esophageal spasms, back injury, indigestion, paresthesia, anxiety, depression, hypothyroidism, migraine, hypertension, ST segment abnormality, urinary retention, GI discomfort, rash.

5.2.3 Other Safety Findings

5.2.3.1 Clinical Laboratory Effects

Clinical laboratory data were obtained at pre- and post-dose visits in many of the Lorex trials, yielding a sample of approximately 500 zolpidem-treated patients with at least some laboratory data. Clinical laboratory data were also obtained at pre- and post-dose visits, and in some cases more frequently, in many of the trials, yielding a sample of

approximately 700 zolpidem-treated patients with at least some laboratory data. The following tables will present, for pools of placebo-controlled studies from the Lorex and databases separately, the proportions of patients meeting arbitrarily defined criteria for changes in laboratory values of possible clinical significance.

5.2.3.1.1 Clinical Chemistry

The following table provides criteria for identifying patients with changes from baseline of possible clinical significance. Only those patients who were relatively normal at baseline and who then exceeded these criterion values at some time on assigned treatment were counted for the proportion tables that follow:

Criteria for Identifying Patients as Having Potentially Clinically Significant Changes in Blood Chemistry Variables

Chemistry Variables	Criterion Values High	Low
BUN	≥ 30 mg/dl	----
Creatinine	≥ 2 mg/dl	----
Total Bilirubin	≥ 2 mg/dl	----
Alkaline Phosphatase	≥ 3 X ULN (U/L)	----
SGOT and SGPT	≥ 3 X ULN (U/L)	----
Uric Acid (Males)	≥ 10.5 mg/dl	----
Uric Acid (Females)	≥ 8.5 mg/dl	----

The following tables provides the actual proportions (n/N, where n = the number of patients exceeding criterion values in the direction of interest while on drug and N = the total number of patients not exceeding criterion values at baseline):

Proportions of Patients Having Potentially Clinically Significant Changes in Blood Chemistry Variables in Placebo-Controlled Zolpidem Studies (< 5 weeks) in the Lorex Program

Chemistry Variables	Zolpidem	Placebo
BUN-H	0/292 (0.0%)	0/147 (0.0%)
Creatinine-H	1/243 (0.4%)	0/117 (0.0%)
T. Bilirubin-H	4/291 (1.4%)	1/146 (0.7%)
Alk. P'Tase-H	0/294 (0.0%)	0/146 (0.0%)
SGOT-H	0/294 (0.0%)	0/147 (0.0%)
SGPT-H	2/275 (0.7%)	0/144 (0.0%)
Uric Acid-H	1/228 (0.4%)	0/117 (0.0%)

Proportions of Patients Having Potentially Clinically Significant Changes in Blood Chemistry Variables in Placebo-Controlled Zolpidem Studies in the LERS Program

Chemistry Variables	Zolpidem	Placebo
BUN-H	5/206 (2.4%)	1/63 (1.6%)
Creatinine-H	4/501 (0.8%)	0/58 (0.0%)
T. Bilirubin-H	1/454 (0.2%)	0/62 (0.0%)
Alk. P'Tase-H	1/476 (0.2%)	1/63 (1.6%)
SGOT-H	0/498 (0.0%)	0/54 (0.0%)
SGPT-H	1/493 (0.2%)	0/51 (0.0%)
Uric Acid-H	2/276 (0.7%)	1/46 (2.2%)

All subjects from the Lorex and programs who met criteria for potentially clinically significant changes in blood chemistry variables were individually examined. None of these changes was accompanied by clinical symptoms and none could be clearly attributed to zolpidem treatment. No patients were discontinued specifically for changes in blood chemistry variables. Neither the comparative data in the tables above nor the inspection of individual cases meeting criterion values suggested any pattern of change in clinical chemistry variables that could be reasonably attributed to zolpidem treatment.

5.2.3.1.2 Hematology

The following table provides criteria for identifying patients with changes from baseline of potential clinical significance. Only those patients who were relatively normal at baseline and who then exceeded these criterion values at some time on assigned treatment were counted for the proportion tables that follow.

Criteria for Identifying Patients as Having Potentially Clinically Significant Changes in Hematology Variables

Hematology Variables	High	Low
Hemoglobin (Males)	----	$\leq$11.5 g/dl
Hemoglobin (Females)	----	$\leq$9.5 g/dl
Hematocrit (Males)	----	$\leq$37%
Hematocrit (Females)	----	$\leq$32%
White Blood Cells	$\geq$16 X $10^3/mm^3$	$\leq$2.8 X $10^3/mm^3$
Neutrophils	----	$\leq$15%
Eosinophils	$\geq$10%	----
Platelets	$\geq$700 X $10^3/mm^3$	$\leq$75 X $10^3/mm^3$

The following tables provide the actual proportions (n/N, where n = the number of patients exceeding criterion values in the direction of interest while on drug and N = the total number of patients not exceeding criterion values at baseline):

Proportions of Patients Having Potentially Clinically Significant Changes in Hematology Variables in Placebo-Controlled Zolpidem Studies (<5 weeks) in the Lorex Program

Hematology Variables	Zolpidem	Placebo
Hgb-L	0/286 (0.0%)	0/144 (0.0%)
Hct-L	2/281 (0.7%)	0/145 (0.0%)
WBC-H or L	1/280 (0.4%)	1/143 (0.7%)
Neutrophil-L	0/290 (0.0%)	0/144 (0.0%)
Eosinophil-H	6/269 (2.2%)	1/134 (0.7%)
Platelet-H or L	0/246 (0.0%)	0/112 (0.0%)

Proportions of Patients Having Potentially Clinically Significant Changes in Hematology Variables in Placebo-Controlled Zolpidem Studies in the LERS Program -

Hematology Variables	Zolpidem	Placebo
Hgb-L	7/507 (1.4%)	0/58 (0.0%)
Hct-L	13/462 (2.8%)	2/58 (3.4%)
WBC-H or L	4/508 (0.8%)	0/58 (0.0%)
Neutrophil-L	0/397 (0.0%)	0/3 (0.0%)
Eosinophil-H	4/394 (1.0%)	0/3 (0.0%)
Platelet-H or L	4/475 (0.8%)	0/46 (0.0%)

All subjects from the Lorex and programs who met criteria for potentially clinically significant change in hematology variables were individually examined. None of these changes was accompanied by clinical symptoms and none could be clearly attributed to zolpidem treatment. Only one patient was discontinued specifically for changes in a hematology variables, i.e., a 26-year-old male whose WBC dropped to 2800 at the lowest point. He had a confounding medical illness that may have played a role. In any case, his WBC returned to normal at some time after stopping zolpidem. Neither the comparative data in the tables above nor the inspection of individual cases meeting criterion values suggested any pattern of change in hematology variables that could be reasonably attributed to zolpidem treatment.

5.2.3.1.3 Urinalysis

There were no discontinuations due to abnormal urinalysis and no pattern of change in urinalysis variables suggestive of any zolpidem effect on these variables.

5.2.3.2 Effects on Vital Signs

Vital signs data were available only for patients in the Lorex program. Blood pressure and heart rate were generally measured pre- and post-dosing in these trials, while body weight and temperature were generally measured only at screening.

The following table provides criteria for identifying patients with changes from baseline of potential clinical significance. Only those patients who were relatively normal at baseline and who then exceeded these criterion values at some time on assigned treatment were counted for the proportion table that follows.

Criteria for Identifying Patterns as Having
Potentially Clinically Significant Changes in
Vital Signs Variables

Vital Signs Variables	Criterion Values* High	Low	Change from BL
Systolic Blood Pressure	180 mmHg	90 mmHg	>= 20 mmHg
Diastolic Blood Pressure	105 mmHg	50 mmHg	>= 15 mmHg
Pulse Rate	120 bts/min	50 bts/min	>= 15 bpm

*: Must meet absolute and change criteria to be considered potentially clinically significant

The following table provides the actual proportions (n/N, where n = the number of patients exceeding criterion values in the direction of interest while on drug and N = the total number of patients not exceeding criterion values at baseline):

Proportions of Patients Having Potentially Clinically Significant Changes in Vital Signs Variables in Lorex Studies

Vital Signs Variables	Zolpidem	Placebo
SBP-Supine (H or L)	19/306 (6%)	1/30 (3%)
DBP-Supine (H or L)	18/306 (6%)	2/30 (7%)
PR-Supine (H or L)	10/224 (4%)	2/30 (7%)
SBP-Sitting (H or L)	46/844 (5%)	43/285 (15%)
DBP-Sitting (H or L)	23/844 (3%)	15/205 (7%)
PR-Sitting (H or L)	49/844 (6%)	24/285 (8%)
SBP-Standing (H or L)	22/329 (7%)	7/52 (13%)
DBP-Standing (H or L)	7/329 (2%)	1/52 (2%)
PR-Standing (H or L)	8/247 (3%)	1/52 (2%)

Neither these data nor an inspection of individual cases meeting criterion values suggested any pattern of change in vital signs variables that could be reasonably attributed to treatment.

5.2.3.3 ECG Effects

ECG data pre- and post-treatment with zolpidem were available for 517 patients participating in Lorex trials. Only one patient had an abnormality for the first time on treatment. This was a 51 year old male with a history of bacterial endocarditis and suspected mitral valve prolapse who was noted to have ST depression 6 and 8 weeks after beginning zolpidem 15 mg. Two days after stopping treatment the abnormality was still present, and a consulting cardiologist considered the abnormality related to the preexisting condition rather than treatment with zolpidem.

5.2.3.4 Special Studies

5.2.3.4.1 Daytime Alertness

The Multiple Sleep Latency Test (MSLT) is an objective test of drowsiness/alertness, and is often used to test subjects on the day following administration of an hypnotic. It involves the measurement of latency to falling asleep during multiple 20-minute test periods, and decreased latencies correlate well with verbal reports of drowsiness. An hypnotic associated with residual sedation might be expected to yield decreased latencies, while an effective hypnotic without carryover effects might be expected to yield increased latencies. The NDA included five double-blind, randomized, placebo-controlled efficacy trials that also involving the use of MSLTs for assessing next day alertness.

In addition, several studies utilized a visual analog scale (VAS) to assess subjectively daytime alertness/drowsiness.

LSH11: This sleep laboratory study involved two independent crossovers (zolpidem 5 mg, zolpidem 15 mg, placebo; and zolpidem 10 mg, zolpidem 20 mg, placebo) in 35 normal, elderly volunteers. Subjects had 4 MSLTs on the day following the second night of treatment, and there were no drug/placebo differences at any time period for either crossover.

Ruther/IGE01: This sleep laboratory study was a 5 period crossover (placebo, zolpidem 10 mg, zolpidem 20 mg, triazolam 0.5 mg, lormetazepam 1 mg) in 10 normal males. Subjects had 5 MSLTs on the day following each night of treatment, and there were no zolpidem/placebo differences. However, there was a significant triazolam/lormetazepam difference. There were no zolpidem/placebo differences on 2 VASs.

Simon/IFR29/35: This was a 3 period crossover (placebo, zolpidem 20 mg, flunitrazepam 2 mg) in 12 normal males. Subjects had 5 MSLTs on the day following each night of treatment, and there was a statistically significant difference between treatments, with zolpidem have the longest mean latency. Zolpidem was not different from placebo on a VAS, but was superior to flunitrazepam on that measure.

Terzano/IIT02: This was a 4-period crossover (placebo or zolpidem 10 mg, with or without 45 db white noise) in 12 normal volunteers. Subjects had 5 MSLTs on the day following each night of treatment. There were no significant between group differences for latency at three of the test periods, however, at 16 and 18 hours after dosing, zolpidem was superior to placebo, i.e., longer latency. There were no significant between group differences on a VAS.

Nicholson/IGB02/08: This was a 5-period crossover (placebo; zolpidem 10, 20, and 30 mg; and diazepam 10 mg) in 6 normal males. Treatment was given at 2:00 pm and alertness was tested at 6.4, 7.5, and 8.5 hours later. There were no significant between group comparisons.

LSH: This was a double-blind, randomized, parallel group sleep laboratory study comparing zolpidem (5, 7.5, 10, 15, and 20 mg) and placebo in subjects with insomnia. There were no significant zolpidem/placebo differences on a VAS assessment of next day drowsiness.

Comment: These studies were not inconsistent with the conclusion that zolpidem, when given at effective hypnotic doses, is not associated with residual sedative effects the next day. However, since it was not clear that some of these trials had sufficient power to detect differences on these measures, they must be considered preliminary trials.

5.2.3.4.2 Psychomotor Testing for Residual Effects

Psychomotor testing is another approach to assessing next day effects of hypnotics. The Digit Symbol Substitution Test (DSST) involves asking subjects to copy symbols into numbered boxes from a list of paired digits and symbols. The Symbol Copying Test (SCT) is a similar assessment for which subjects must copy the symbol from the box above to the empty box below. These tests are timed and the score is the number completed

correctly. Reaction time tasks may involve simple reaction time, e.g., the Critical Flicker Fusion Test (CFF), or a more complex reaction task, e.g., the Complex Reaction Time Test (CRT). The NDA included seven double-blind, randomized, placebo-controlled efficacy trials which also involved psychomotor testing of next day effects.

Simon/IFR29/35: This was a 3 period crossover (placebo, zolpidem 20 mg, flunitrazepam 2 mg) in 12 normal [illegible]s. There were no zolpidem/placebo differences on the following next da[illegible]ests: DSST, CRT, or CFF. However, both zolpidem and placebo were superior to flunitrazepam on all three tests.

Grilliat/IFR22: This was a 3-period cross[illegible]ver (placebo, zolpidem 20 mg, triazolam 0.5 mg) in 9 normal volunteers. Next day psychomotor testing included: simulated driving; a coding test similar to the DSST; an auditory reaction time test; a visual reaction time test; and a proofreading test. There were no significant drug/placebo differences for any of these tests. However, zolpidem was superior to triazolam on the driving test.

LSH02: This sleep laboratory study was a 6-period crossover (zolpidem 2.5, 5, 7.5, 10, and 20 mg; and placebo) in 12 normal males. Treatments were each given for two consecutive nights, and next day psychomotor testing included: DSST, SCT, SRT, and CRT. While there was a significantly slower reaction time on the SRT for zolpidem 20 mg compared to placebo on the second night of administration, there were no other significant drug/placebo differences for these tests.

LSH11: This sleep laboratory study involved two independent crossovers (zolpidem 5 mg, zolpidem 15 mg, placebo; and zolpidem 10 mg, zolpidem 20 mg, placebo) in 35 normal, elderly volunteers. Treatments were each given for two consecutive nights, and next day testing was done with the DSST. Zolpidem was worse than placebo for all doses on the morning following the second night of treatment.

LSH This was a double-blind, randomized, single-dose, parallel group sleep laboratory study comparing zolpidem (5, 7.5, 10, 15, and 20 mg) and placebo in 462 subjects with insomnia. There were no zolpidem/placebo differences on next day testing (DSST and SCT) for any of the doses.

LSH : This was a double-blind, randomized sleep laboratory study comparing several fixed doses of zolpidem with placebo in 31 subjects experiencing sleep difficulty resulting from a 3-hour phase advance of their bedtime. It consisted of two independent 3-period crossovers as follows: I (placebo, zolpidem 10 and 20 mg); II (placebo, zolpidem 5 and 15 mg). Dosing with assigned treatment was on the night of phase advance, and next day psychomotor testing included DSST and SCT. There were no significant zolpidem/placebo differences for either of these tests.

LSH This was a double-blind, randomized, 35-night parallel group study of two doses of zolpidem (10 and 15 mg) and placebo in 75 patients with

insomnia. Subjects were in a sleep laboratory for the first two nights of each week, and had DSST and SCT done on the mornings following each of those two nights. There were no significant zolpidem/placebo differences at any week for either of these measures.

Comment: Except for a finding of slower reaction time for zolpidem 20 mg compared to placebo in one of the six studies in non-elderly adults, there was no evidence for next day decrements in psychomotor function associated with treatment with zolpidem on the previous night. However, the study in elderly adults did reveal a statistically significant decrement in DSST for all zolpidem doses compared with placebo on the day following second night of treatment.

5.2.3.4.3 Rebound Insomnia

Rebound insomnia is said to occur when (1) individuals with insomnia that has responded to treatment with an hypnotic experience a recurrence of insomnia upon discontinuation of the drug, or (2) individuals with insomnia experience, upon discontinuation of an hypnotic, insomnia of even greater severity than that experienced prior to hypnotic treatment. This NDA included data from 4 double-blind, randomized, placebo-controlled efficacy trials that provided a separate analysis of the first post-treatment night, thus permitting an evaluation for rebound insomnia.

LSH02: This sleep laboratory study was a 6-period crossover (zolpidem 2.5, 5, 7.5, 10, and 20 mg; and placebo) in 12 normal males. Treatments were each given for two consecutive nights, followed by placebo on the third night to assess post-treatment effects. There were no zolpidem/placebo differences in polysomnographic (PSG) or subjective measures of sleep function on the post-treatment night.

LSH11: This sleep laboratory study involved two independent crossovers (zolpidem 5 mg, zolpidem 15 mg, placebo; and zolpidem 10 mg, zolpidem 20 mg, placebo) in 35 normal, elderly volunteers. Treatments were each given for two consecutive nights, followed by placebo on the third night to assess post-treatment effects. There were scattered findings of significantly worse PSG measures of sleep function for zolpidem compared to placebo on the post-treatment night: sleep efficiency decreased for zolpidem 15 mg; number of awakenings increased for zolpidem 10 and 20 mg. However, there was a more consistent pattern of significantly more subjective complaints of disturbed sleep for zolpidem compared to placebo on the post-treatment night: poorer quality of sleep, more difficulty in falling asleep, and less refreshing sleep for zolpidem 10, 15, and 20 mg; more awakenings for zolpidem 15 and 20 mg; and shorter latency for zolpidem 15 mg.

LSH : This was a double-blind, randomized, 35-night parallel group study of two doses of zolpidem (10 and 15 mg) and placebo in 75 patients with insomnia. Rebound was assessed during three placebo post-treatment nights following the 5 weeks of treatment. Of all the PSG measures tested, the only significant finding was for a greater wake time

during sleep for zolpidem 15 mg compared to placebo, and only on the first post-treatment night. There were scattered findings of significantly more subjective complaints of disturbed sleep for zolpidem compared to placebo on the first post-treatment night only: poorer sleep quality and greater morning sleepiness for zolpidem 15 mg.

LSH This was a double-blind, randomized, 31-night parallel group study of two doses of zolpidem (10 and 15 mg) and placebo in 145 patients with insomnia. Rebound was assessed by subjective questionnaire only during four placebo post-treatment nights following the 31 days of treatment. The only significant zolpidem/placebo difference in sleep function was a greater decrease from baseline in subjective total sleep time for zolpidem 15 mg.

Comment: These studies yielded only weak evidence for rebound insomnia in association with discontinuation from zolpidem, primarily involving subjective complaints rather than objective PSG measures and only on the first post-treatment night. These findings were most compelling in the elderly population, suggesting either a greater pharmacodynamic sensitivity to such effects in the elderly or age-related pharmacokinetic differences.

5.2.3.4.4 Memory Effects

The NDA included three studies adequate in design and conduct for an evaluation of the memory effects of zolpidem. These were all double-blind, randomized, placebo-controlled hypnotic efficacy studies of normal volunteers that included special assessments of memory function.

LSH11: This sleep laboratory study involved two independent crossovers (zolpidem 5 mg, zolpidem 15 mg, placebo; and zolpidem 10 mg, zolpidem 20 mg, placebo) in 35 normal, elderly volunteers. Treatments were given for two consecutive nights, and memory was tested each night and the following day with the Buschke Memory Test. A list of items was presented 20 minutes after each dosing, with recall being requested at bedtime (immediate recall) and in the morning (delayed recall). A second list was presented in the morning, with recall being requested in 10 minutes (immediate recall). Of the numerous zolpidem/placebo contrasts, there was only one significant comparison with placebo, i.e., reduced immediate recall of the second list in the morning after the second zolpidem 15 mg dose.

Simon/IFR29/35: This was a 3 period crossover (placebo, zolpidem 20 mg, flunitrazepam 2 mg) in 12 normal males. There were two memory tests the morning after dosing: a paired associate learning test with immediate recall, and a test requiring retention of 12 pictures for 30 minutes after presentation. While there were no significant zolpidem/placebo differences, there were numerous significant comparisons with flunitrazepam and both zolpidem and placebo, all arising from poorer performance with flunitrazepam.

Grilliat/IFR22: This was a 3-period crossover (placebo, zolpidem 20 mg, triazolam 0.5 mg) in 9 normal volunteers. Memory testing on the morning after dosing included a test of immediate recall (digit span) and two tests of delayed recall: a word list presented to subjects on the evening after dosing and recalled the next morning; and a similar exercise using a time table. Other testing included morning recall of a phone call received 30 minutes after dosing the previous evening, and several other tests of delayed recall of information presented the next morning and recalled later in the day. There were no statistically significant drug/placebo differences on any of the comparisons for any of the tests.

Comment: While these studies yielded no findings suggestive of a compromise of immediate or delayed recall secondary to zolpidem use, Dr. Lee cites in her review a drug abuse study (Griffiths) that did find impaired memory for both zolpidem and triazolam. I was also surprised by the negative findings for triazolam in the Grilliat study, since there are numerous positive studies for that drug, particularly at a 0.5 mg dose. Thus, I question the sensitivity of that study. Nevertheless, the data available for zolpidem do not suggest a prominent memory effect.

5.2.3.4.5 Respiratory Function

Several studies were conducted to assess the effects of zolpidem on respiratory function in normal volunteers.

LSH04: This was a 4-period crossover study (zolpidem 10 and 20 mg, codeine phosphate 60 mg, and placebo) in 12 normal males. Respiratory drive was evaluated by respiratory response to CO_2 challenge and by respiratory inductive plethysmography. Neither zolpidem dose affected ventilatory response during wakefulness. While zolpidem 20 mg produced a decrease in mean inspiratory flow during sleep, the decrease was within the range associated with normal, unmedicated sleep.

Maillard/IFR27: This was a 4-period crossover study (zolpidem 10 and 20 mg, diazepam 10 mg, and placebo) in 16 normal volunteers. There were no effects of treatment on ventilatory drive as assessed by CO_2 challenge.

LSH03: This was a single-blind, tolerance study of single morning doses of zolpidem 20-90 mg given to 15 normal volunteers in 8 weekly sessions, in increments of 10 mg/week. THere was continuous recording of PSG, O_2 saturation, and respiratory rate from 10 minutes before drug administration until wakefulness. While there were instances of O_2 desaturation, there was no relationship of dose to number, intensity or duration of desaturations. This study was difficult to evaluate without a placebo control group.

LSH06: This was a parallel groups trial comparing respiratory response to CO_2 challenge after single doses of zolpidem 20 mg (N=31), codeine phosphate 60 mg (N=29), and placebo. No respiratory suppression was observed.

Two studies evaluated zolpidem in subjects with some degree of sleep apnea, and a third involved patients with respiratory failure.

Cirignotta/IIIT06: This study evaluated the effects of zolpidem 20 mg in 12 subjects with sleep apnea. There was an increase in the number, but not the duration, of apneas and hypopneas. PaO_2 was significantly less for zolpidem compared to placebo, but the mean remained above 88%.

Kurtz/IFR38: This study evaluated the effects of zolpidem 10 mg in 12 elderly subjects with a mild degree of sleep apnea. The number of apneas was increased over baseline on the first night of treatment, but not on the seventh night. This study was difficult to evaluate without a placebo control.

Lemercier/IIER17: This was an open study of zolpidem 20 mg in 10 patients with chronic respiratory failure (PaO_2 < 60 mmHg). There was too much variability in measures of respiratory function to draw any conclusions from this study. However, despite substantial drowsiness, O_2 saturation 2 and 5 hours after zolpidem administration was within the range observed on the 4 previous days for all but one patient.

Comment: In the aggregrate, these studies do not suggest any prominent effect of zolpidem on respiratory function. However, they are too preliminary to warrant any conclusions regarding zolpidem's safety in individuals with compromised respiratory function.

5.2.3.4.6 Endocrine Function

Two studies included sampling of hormone levels in subjects exposed to zolpidem.

Emeriau/IFR25: Four healthy elderly subjects (2 male, 2 female) had frequent blood sampling during a 24-hour period following a single oral zolpidem 20 mg dose. No effect was seen on the following hormone assays: FSH, LH, prolactin, TSH, GH, or cortisol.

Colle/IFR42: This was a double-blind, randomized, 2-period crossover study (zolpidem 10 mg, placebo) in 12 normal males. No effect was seen on the following hormone assays: GH, LH, prolactin, cortisol, ACTH, FSH, testosterone, T3, T4, or TSH.

Comment: Although these studies revealed no effects on a number of endocrine systems, these results must be considered preliminary.

5.2.3.4.7 Premedicant Studies

Zolpidem was studied as a premedicant in the program. There were 12 studies in adults, involving N=604 subjects who received zolpidem, and one study in children, involving N=99 subjects who received zolpidem. Generally subjects received zolpidem one hour prior to surgery. The adult zolpidem doses ranged from mg and the pediatric zolpidem doses ranged from mg/kg. Zolpidem was generally well tolerated in

the adult studies at doses up to 20 mg, and the predicted effects of sedation and amnesia were obtained. Adverse events reported more commonly for zolpidem than placebo included dizziness/vertigo, diplopia, nausea and vomiting. Zolpidem was less well tolerated than diazepam in the pediatric studies, with particular complaints including diplopia and visual disturbances, vomiting, and hallucinations.

5.2.3.5 Other Adverse Events

In the Integrated Safety Summary, the sponsor provided a number of adverse event incidence tables for the Lorex database, including tables pooled across all studies, across only controlled studies, and across short term and long term study pools separately. In an October 15, 1991 submission, the sponsor provided additional information pertinent to the 'Adverse Reactions' section of labeling. Tables were provided with a breakdown by dose, by age, by weight, and by sex. In this overview, I will focus on two tables providing incidence data for the placebo controlled short term studies (2, 8, 9, and 11) and the placebo controlled long term studies (17 and 19) separately. I will provide data on dose response for selected events.

5.2.3.5.1 Commonly Observed

During short term treatment (1-2 nights) with Ambien at doses up to 10 mg, the most commonly observed adverse events associated with the use of Ambien and not seen at an equivalent incidence among placebo treated patients were: drowsiness and nausea. [Note: These were the two of three events occurring at an incidence of $\geq$ 1% for Ambien and not seen for placebo.] During longer term treatment (31-35 nights) with Ambien at doses up to 10 mg, the most commonly observed adverse events associated with the use of Ambien and not seen at an equivalent incidence among placebo treated patients were: drowsiness, dizziness, lethargy, drugged feeling. [Note: The rule I used here was to include those events that occurred at an incidence of at least 4% for Ambien and for which the incidence for Ambien was approximately 1.5 fold or greater than the incidence for placebo.]

5.2.3.5.2 Associated with Discontinuation of Treatment

It was difficult to develop the information needed for this subsection, in part because the sponsor did not provide the tables needed to profile patients dropping out for adverse events. However, we do know the totals dropping out for adverse events for each of the Lorex (51/940 = 5%) and the LERS (77/1320 = 6%) populations. In addition, an examination of the descriptions of dropouts from each of these databases revealed that most commonly patients leaving these trials for adverse events were experiencing daytime drowsiness, dizziness, impaired coordination and sometimes, amnesia, i.e., predicted CNS events for this class of drugs. Consequently, I think it would be fair to characterize adverse dropouts from these trails as follows:

Approximately 5% of 940 patients who received Ambien in US premarketing clinical trials and approximately 6% of 1320 patients who received Ambien in foreign premarketing clinical trials discontinued treatment because of an adverse clinical event. Events commonly associated with discontinuation were daytime drowsiness, dizziness, impaired coordination and amnesia.

5.2.3.5.3 Incidence in Controlled Clinical Trials

The following table was provided by the sponsor in the October 15, 1991 submission. This table was derived from a pool of all 4 of the placebo controlled short term efficacy trials involving zolpidem. These trials involved normal males who were experiencing experimentally induced insomnia and were treated for 1-2 nights with zolpidem in doses ranging from mg. The table is limited to data from doses only up through 10 mg, since that is the highest dose that will be recommended in labeling. It includes only adverse events occurring at an incidence of at least 1% for zolpidem patients.

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

Body System/ Adverse Event*	Ambien (≤ 10 mg) (N=335)	Placebo (N=179)
Central and Peripheral Nervous System		
Headache	2	3
Drowsiness	1	-
Gastrointestinal System		
Nausea	1	-

*Events reported by at least 1% of Ambien patients are included.

Comment: The adverse events appearing to be related to zolpidem treatment fall in the CNS and GI systems, and the rates are quite low.

The following table was provided by the sponsor in the October 15, 1991 submission. This table was derived from a pool of the two placebo controlled long term efficacy trials involving zolpidem. These trials involved patients with chronic insomnia who were treated for 31-35 nights with zolpidem in doses of 10 or 15 mg. The table is limited to data from doses up to and including 10 mg, since that is the highest dose recommended for use. It includes only adverse events occurring at an incidence of at least 1% for zolpidem patients.

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

Body System/ Adverse Event*	Ambien (≤ 10 mg) (N=70)	Placebo (N=77)
Autonomic Nervous System		
Dry Mouth	3	1
Body as a Whole		
Allergy	3	-
Chest Pain	1	-
Fatigue	1	3
Fever	1	4
Influenza-like Symptoms	1	-
Central and Peripheral Nervous System		
Headache	20	25
Drowsiness	11	7
Dizziness	7	3
Lethargy	7	1
Drugged Feeling	4	-
Amnesia	3	-
Light-Headed	3	-
Agitation	1	1
Anxiety	1	-
Ataxia	1	-
Confusion	1	-
Decreased Cognition	1	-
Depression	1	1
Hypoasthesia	1	-
Insomnia	1	3
Panic Attack	1	-
Sleep Disorder	1	-
Gastrointestinal System		
Dyspepsia	4	3
Nausea	4	4
Anorexia	3	-
Diarrhea	3	3
Constipation	1	-
Flatulence	1	-
Hematologic and Lymphatic System		
Lymphadenopathy	1	-
Immunologic System		
Infection	1	-
Musculoskeletal System		
Myalgia	4	4

Arthralgia	3	5
Reproductive System		
Dysmenorrhea	1	1
Respiratory System		
Sinusitis	6	3
Pharyngitis	3	3
Laryngitis	1	-
Upper Respiratory Infection	1	3
Skin and Appendages		
Rash	1	-
Special Senses		
Abnormal Taste	1	-
Urogenital System		
Urinary Tract Infection	3	1

*Events reported by at least 1% of patients treated with Ambien

Comment: As was true of the short term experience, patients exposed to zolpidem more chronically also experienced apparently zolpidem related adverse events primarily in the CNS and GI systems. Overall, event rates were higher during chronic exposure, for both drug and placebo patients, as would be expected.

In the following two tables, modified from tables II.B.4 and II.B.5 of the Integrated Safety Summary (Vol 1.54), incidence data for selected adverse events are presented by dose category for each of the short term and long term pools. The specific events included were selected because of an apparent dose response relationship for those events.

INCIDENCE OF SELECTED ADVERSE EXPERIENCES BY DOSE IN SHORT TERM PLACEBO-CONTROLLED CLINICAL TRIALS
(Percentage of Patients Reporting)

		Ambien Dose				
Adverse Experience	Placebo N=179	5.0 mg N=97	7.5 mg N=114	10 mg N=148	15 mg N=84	20 mg N=95
Dizziness	-	-	-	1	-	3
Drowsiness	-	1	-	2	5	7
Nausea	-	1	2	1	2	5
Vomiting	-	-	1	-	2	3
Amnesia	-	-	-	-	-	4

INCIDENCE OF SELECTED ADVERSE EXPERIENCES BY DOSE IN LONG TERM PLACEBO-CONTROLLED CLINICAL TRIALS
(Percentage of Patients Reporting)

Adverse Experience	Placebo N=77	Ambien Dose 10 mg N=70	Ambien Dose 15 mg N=68
Confusion	-	1	4
Dizziness	3	7	10
Drowsiness	7	11	15
Dyspepsia	3	4	7
Nausea	4	4	7

Comment: These data are strongly suggestive of a dose response relationship for at least certain of the adverse events associated with zolpidem use.

5.2.3.5.4 Incidence Across Entire Pre-Marketing Data Base

In the October 15, 1991 submission, the sponsor provided a subsection for the 'Adverse Reactions' section of labeling entitled 'Adverse Event Incidence Across the entire Clinical Trial Database.' They clarified that events for this listing included all treatment emergent adverse events reported for all the patients exposed to zolpidem in the Lorex and LERS databases, i.e., a total of 940 + 1320 = 2260. Events for this listing were expressed as preferred terms using a modification of the WHO dictionary of preferred terms. Events are broken out by frequency in this listing, i.e., frequent, infrequent, and rare. This listing is acceptable for the purposes of labeling, except that they have included events already provided in the 1% table. Consequently, I have revised this listing by deleting those redundant terms.

5.2.4 Explorations for Potential Interactions

5.2.4.1 Drug-Drug Interactions

5.2.4.1.1 Alcohol

Coupez/1BE04: This was a double-blind, 6-period crossover [zolpidem 20 mg, triazolam 0.5 mg, placebo, each administered twice, once with alcohol in juice (0.6 ml alcohol/kg) and once with juice alone] in 12 normal males. Tests 30 minutes post-dosing included: proofreading; Stroop test; tapping test; bead stringing; memory test; and visual analog scales for drowsiness, etc. Both drugs reduced performance on the various performance measures compared to placebo. However, there was no effect from alcohol by itself and no interaction between alcohol and the two drug treatments. There was no effect of alcohol on plasma concentrations of zolpidem or triazolam.

Thebault: This was a double-blind, 6-period crossover [zolpidem 20 mg, flunitrazepam 2 mg, placebo, each administered twice, once with alcohol

(6.5 ml wine/kg) and once without] in 12 normal males. The wine was consumed with supper prior to drug administration before bedtime, and performance testing the following morning included: visual and auditory reaction times, proofreading, Stroop test, critical flicker fusion, and driving simulation. There was no zolpidem/placebo difference for any of the tests and generally no alcohol effect or interaction.

Comment: While the Coupez study did not demonstrate an interaction of zolpidem with alcohol, the lack of an effect of alcohol by itself raises a question about the sensitivity of this study to detect an interaction effect, and consequently, this study provides only minimal reassurance about the possibility of an interaction of zolpidem with alcohol. It would have been unlikely to find any alcohol interaction effects in the Thebault study in which performance testing was done on the following day, many hours after alcohol consumption.

5.2.4.1.2 Caffeine

Vandel: This was a double-blind, 4-period crossover (caffeine 300 mg or placebo, followed in 45 minutes by zolpidem 20 mg or placebo, before bedtime) in 8 normal adults. Subjective assessment of sleep quality revealed no detrimental effect of prior caffeine administration on zolpidem's hypnotic efficacy, while caffeine preceding placebo resulted in insomnia in 5 of 8 subjects.

5.2.4.1.3 Other Psychotropic Drugs

Coupez/Imipramine: This was an open, 3-period crossover study (zolpidem 20 mg, imipramine 75 mg, and the combination) in 6 normal males. There were no significant between group differences on a visual analog scale of vigilance, however, reports of drowsiness were worst with the combination, compared to either drug alone. Pharmacokinetic variables were mostly unaffected by the combination, except for imipramine Cmax, which was significantly decreased (about 20%) with the combination.

Harvengt/IBE03/Chlorpromazine: This was a 2-period crossover study (zolpidem 20 mg alone, zolpidem 20 mg plus chlorpromazine 50 mg) in 6 normal volunteers. There was no significant effect of chlorpromazine on zolpidem pharmacokinetics. The combination of chlorpromazine with zolpidem produced additive effects of decreased alertness and decreased psychomotor performance.

Lambert/IFR21/Haloperidol: This was a 3-period crossover study (zolpidem 20 mg, haloperidol 2 mg, and the combination) in 6 normal volunteers. There was no significant effect of haloperidol on zolpidem pharmacokinetics. There were no between group differences on a visual analog scale for drowsiness.

Forster/ICH05/Flumazenil: This was a double-blind, 4-period crossover study [zolpidem 0.21 mg/kg iv (or its placebo), followed by flumazenil, a benzodiazepine antagonist, 0.04 mg/kg (or its placebo)] in 9 normal males. While there was no statistically significant pharmacokinetic

interaction, there was a trend toward smaller AUCs after zolpidem with flumazenil compared to zolpidem alone.

5.2.4.1.4 Other Drugs

Harvengt/IBE05/Cimetidine and Ranitidine: This involved two separate open sequences, one for each of these two H_2 blockers, during which 6 normal volunteers were given single doses of zolpidem 20 mg (1) alone, (2) after 1 day of H_2 treatment, and (3) after 17 days of H_2 treatment. Doses of H_2 blockers were as follows: cimetidine 200 mg tid and 400 mg hs; ranitidine 150 mg bid. Neither cimetidine nor ranitidine had an effect on zolpidem pharmacokinetics or pharmacodynamics.

Meyer/IFR39/Digoxin: This was an open trial involving a sequence of digoxin by itself (0.25 mg q 8:00 am for 7 days), followed by digoxin plus zolpidem (digoxin 0.25 mg q 8:00 am plus zolpidem 10 mg q hs, for 7 days) in 10 normal males. There were no between period differences in digoxin Cmax or AUC.

Warrington/IGB05/Warfarin: This was an open trial involving a sequence of warfarin by itself for 10 days (at doses sufficient to prolong prothrombin time to 1.5 times baseline value), followed by warfarin plus zolpidem (zolpidem 20 mg hs) for 4 days, in 8 normal males. Prothrombin times were unchanged by the addition of zolpidem.

Albin/IFR24/Antipyrine: This was an open study of antipyrine pharmacokinetics in 12 normal males given zolpidem 20 mg q hs for 15 nights. Antipyrine 1 mg was given before and after zolpidem treatment. Antipyrine pharmacokinetics were unchanged by zolpidem administration.

5.2.4.2 Drug-Disease Interactions

Collignon/IIBE02/Coronary Insufficiency: This was an open trial involving the administration of zolpidem 10 mg to 11 subjects with coronary insufficiency undergoing cardiac catherization. There were no clinically significant changes in hemodynamic parameters measured before and after zolpidem administration.

Bercoff/IFR20/Hepatic Disease: This was an open trial involving single oral dosing with zolpidem 20 mg in two groups of 8 each: normal subjects and subjects with hepatic cirrhosis. There were approximately 5-fold increases in zolpidem AUC and half-life and a 2-fold increase in Cmax for the cirrhotic patients compared to the normals.

Bouchet/IFR12/Renal Disease: This was an open trial involving dosing with zolpidem (10 mg, by iv infusion over 20 minutes) in 24 subjects with impaired renal function: 16 on dialysis (8 received zolpidem 3 hours before dialysis, and 8 recieved zolpidem between dialysis sessions); 8 with chronic renal failure not requiring dialysis. While both half-life and AUC for zolpidem were numerically increased for the renally compromised patients compared to a healthy control group, the differences were not statistically significant for these parameters. However, there

was a statistically significantly greater volume of distribution for the renally impaired group. This study does not permit a definitive conclusion about the effects of renal disease on zolpidem pharmacokinetics after oral dosing.

Pointel/IFR43/Obesity: This was an open trial in which 20 obese subjects were given zolpidem 10 mg, first by tablet orally, and 2 days later by a 15 minute iv infusion. The pharmacokinetic results of this trial were compared with pharmacokinetic parameters derived from dosing with 10 mg orally in lean subjects in a prior study. Both the mean elimination half-life and the mean volume of distribution were increased by approximately 50% in the obese subjects compared to the lean subjects, resulting in essentially no change in total body clearance between the two groups. Cmax was decreased by approximately 50% for the obese group compared to the lean group. The clinical significance of the lower and later peak zolpidem concentration for the obese subjects is unknown.

Respiratory Disease: Three studies involving subjects with impaired respiratory function were described under 'Special Studies.'

5.2.4.3 Drug-Demographic Interactions

5.2.4.3.1 Age/Pharmacokinetic Interactions

Emeriau/IFR25/Elderly: This was an open trial involving the administration of a single zolpidem 20 mg dose to 8 elderly subjects ranging in age from Frequent blood samples were obtained for pharmacokinetic analysis, and the results were compared to data obtained from young adults in a prior study. Mean Cmax, half-life and AUC values were increased 50%, 32%, and 64% respectively in the elderly compared to the younger adults, and all differences were statistically significant.

Kurtz/IFR38/Elderly: This was an open trial involving dosing with zolpidem 10 mg q hs for 7 days in 11 subjects ranging in age from Blood samples for pharmacokinetic analysis were obtained after the first and seventh doses. There was no significant difference between PK parameters on days 1 and 7, and no evidence for accumulation.

Forette/IFR34/Elderly: This was an open, 2-way crossover study (single zolpidem 10 mg doses, separated by 1 week interval: oral dose; 20 minute iv infusion) in 9 subjects ranging in age from Frequent blood samples were obtained for pharmacokinetic analysis, and the results were compared to data obtained from young adults in a prior study. Although absolute bioavailability was decreased by about 20% in the elderly compared to the younger adults, the AUC was approximately 3-fold greater in the elderly, probably because of a substantial decrease in the clearance for the elderly compared to the young.

Colle/IFR44/Children: This study involved the single dose, oral administration of zolpidem 10 mg to 6 children ranging in age from Blood samples were obtained frequently for pharmacokinetic analysis. Clearance was 2-3 times greater than values typically seen in adults, and

Cmax, AUC and half-life were all decreased compared to values seen in adults.

5.2.4.3.2 Age/Pharmacodynamic Interactions

There was a clear age dependency for treatment emergent adverse experiences associated with zolpidem treatment, i.e., in a pool of controlled trials, the incidences for such events overall were 16% in the ≤24 group, 23% in the 25-49 group, and 41% in the ≥50 group. The age differences were particularly prominent for the events drowsiness, headache, lethargy, myalgia and amnesia. Age related pharmacokinetic differences may in part account for these differences.

5.2.4.3.3 Sex/Pharmacodynamic Interactions

Overall, adverse event reporting rates in females were approximately twice those seen in males. These differences may not be explained by weight differences between males and females, since similar differences were not seen in patients categorized by weight.

5.2.5 Drug Abuse and Dependence

5.2.5.1 Studies of Abuse Potential

There were two principal studies in the NDA focused on evaluating the abuse potential of zolpidem. Both studies compared single doses of zolpidem with a benzodiazepine and placebo on a variety of subjective and objective measures of psychotropic effect.

LSH14/Jasinski: This was a double-blind, crossover study [6x6 latin square with 3 zolpidem doses (10, 20, and 40 mg), 2 diazepam doses (10 and 20 mg), and placebo] in 12 male volunteers with a history of substance abuse Subjects were on a research ward and received one dose per day for six consecutive days. Subjects were dosed in the morning and then assessed over the course of the day on a variety of subjective and objective instruments for measuring subjective drug experience, 'likeness' to known drugs of abuse, 'likeability,' sedative effect, etc. Overall, the results suggested that the subjective effects of zolpidem were similar to those of diazepam. Zolpidem 40 mg was considered equivalent to diazepam 20 mg in subjective effect on many, but not all, measures. It was difficult to distinguish zolpidem 10 mg from placebo. Thus, this study was suggestive of an abuse liability of the benzodiazepine type in association with zolpidem.

Comment: The reviewer from the Drug Abuse Unit who evaluated this study had a number of criticisms, particularly with regard to the analysis. He objected to the focus on an 'AUC' approach for looking at the first three hours after drug administration, since he felt that such an approach would not permit the discrimination of possibly important differences between the two active drugs very early after drug administration. He had a number of other comments as well, all of which were sent to the sponsor on 2-7-91, and the sponsor has responded to these comments. From the

standpoint of a safety evaluation and labeling, I consider the data sufficient as is to proceed with an approvable action.

LSH16/Griffiths: This was a double-blind, crossover study [zolpidem 15, 30, and 45 mg; triazolam 0.25, 0.5 and 0.75 mg, placebo] in 15 adult males with a history of sedative abuse. Subjects were outpatients and received one dose per day for seven consecutive days. Subjects were dosed in the morning and then assessed over the course of the day on a variety of subjective and objective instruments for measuring subjective drug experience, 'likeness' to known drugs of abuse, 'likeability,' sedative effect, memory impairment, etc. Overall, the results suggested that there was a dose related effect on psychometric test that was, for the most part, similar for the two active drugs. However, in general, the memory impairment for triazolam was greater than for zolpidem. Zolpidem 45 mg was more frequently identified as something other than a sedative/hypnotic, perhaps because of a number of dysphoric effects seen at this dose, including vomiting.

Comment: This study also tends to provide support for the view that zolpidem has potential for abuse of the benzodiazepine type. However, its dysphoric effects at higher doses may limit this potential.

5.2.5.2 Potential for Physical Dependence

While there is little direct evidence for a potential for physical dependence in association with the administration of zolpidem, given its similarity pharmacologically to other drugs in the sedative/hypnotic class, it is likely that it too has such potential.

5.2.6 Human Reproduction Data

There were no adequate and well-controlled studies of zolpidem in pregnant women.

5.3 Clinical Sections of Labeling

Note: In this section, I will comment on the clinical sections and subsections of labeling proposed in the 5-17-91 draft by Lorex, and in a 10-15-91 addendum.

5.3.1 Clinical Pharmacology

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

The sponsor has not included this subsection that is now common to all recently approved benzodiazepine hypnotics, presumably because zolpidem structurally is not a benzodiazepine. However, zolpidem is similar enough in its pharmacology to benzodiazepines that, in my view, the standard language regarding elimination rate and adverse effects belongs in this labeling as well. Consequently, I propose adding a modification of the standard language, i.e., by deleting the term benzodiazepine, as follows:

> "The type and duration of hypnotic effects and the profile of unwanted effects during administration of hypnotic 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 hypnotics may develop. If the drug has a short elimination half-life, it is possible that a relative deficiency of the drug or its active metabolites (i.e., in relationship to the receptor site) may occur at some point in the interval between each night's use. This sequence of events may account for two clinical findings reported to occur after several weeks of nightly use of rapidly eliminated hypnotics, namely, increased wakefulness during the last third of the night, and the appearance of increased signs of daytime anxiety."

Controlled Trials Supporting Efficacy and Safety

Rather than trying to fix the sponsor's proposal for this subsection, I propose the following as an alternative:

> "Normal adults experiencing transient insomnia during the first night in a sleep laboratory were evaluated in a double-blind, parallel group, single-night trial comparing 2 doses of zolpidem (7.5 and 10 mg) and placebo. Both zolpidem doses were superior to placebo on (1) objective (polysomnographic) measures of sleep latency, sleep efficiency, and number of awakenings, and on (2)

subjective measures of sleep latency and sleep quality, but not sleep duration.

Adult outpatients with chronic insomnia were evaluated in a double-blind, parallel group, 5-week trial comparing 2 doses of zolpidem (10 and 15 mg) and placebo. On objective (polysomnographic) measures of sleep latency and sleep efficiency, zolpidem was superior to placebo for all 5 weeks for zolpidem 15 mg and for the first 4 weeks for zolpidem 10 mg. However, neither zolpidem dose was superior to placebo on objective measures of number of awakenings. On a subjective measure of sleep latency, zolpidem 15 mg was superior to placebo for all 5 weeks and zolpidem 10 mg for only weeks 2 and 3. Zolpidem was less consistently superior to placebo on other subjective measures of hypnotic effect.

Adult outpatients with chronic insomnia were evaluated in a double-blind, parallel group, 4-week trial comparing 2 doses of zolpidem (10 and 15 mg) and placebo. Zolpidem 10 was superior to placebo on a subjective measure of sleep latency for all 4 weeks, but on subjective measures of total sleep time, number of awakenings, and sleep quality only for the first treatment week. Zolpidem 15 mg was superior to placebo on a subjective measure of sleep latency for the first 3 weeks, on a subjective measure of total sleep time for only the first week, and on number of awakenings and sleep quality only for the first 2 treatment weeks."

Preliminary studies utilizing objective measures of daytime sleepiness (multiple sleep latency tests) and patient ratings of alertness yielded no evidence of residual next-day effects after bedtime administration of Ambien. However, psychomotor performance testing did reveal some next-day impairment after bedtime dosing with Ambien, especially in the elderly.

In studies evaluating sleep on the nights following discontinuation of Ambien, there was little polysomnographic evidence of rebound insomnia at recommended doses. However, there was subjective evidence of impaired sleep on the first post-treatment night, especially in the elderly.

While preliminary studies utilizing objective measures of memory yielded little evidence for memory impairment following the administration of Ambien, there was more subjective evidence from other clinical trials for anterograde amnesia occurring in association with the administration of Ambien.

5.3.2 Indications and Usage

The sponsor has proposed language that I feel goes beyond the data. In particular, they make a claim for short-term, and insomnia, and they claim lack of tolerance to hypnotic effects in controlled trials of up to 3 months and open trials of up to 6 months. In my view, the longer term controlled trials data and the open trial data

are uninterpretable from the standpoint of both efficacy and tolerance. Any interpretable data with regard to the issue of persistence of beneficial effects are presented in the Clinical Pharmacology section and do not need to be duplicated here. In addition, they have omitted standard language cautioning that prolonged treatment is generally not necessary or recommended, and that insomnia may be a symptom of another disorder.

We have recently made major revisions in the labeling for currently marketed benzodiazepine hypnotics, including a substantially revised Indications section. These revisions have emphasized the need for careful evaluation of patients presenting with insomnia and the desirability of short-term treatment. I think that the revised Indications section would be appropriate for zolpidem as well. Consequently, I propose the following as an alternative to the sponsor's section:

> "Ambien (zolpidem) 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 Ambien should be written for short-term use (7-10 days) and it should not be prescribed in quantities exceeding a 1-month supply."

5.3.3 Contraindications

The sponsor has proposed a statement contraindicating Ambien in patients with known hypersensitivity. However, such statements are appropriate only if there is actual evidence of hypersensitivity. A statement should be imbedded in the proposed labeling asking the sponsor to comment on this issue.

For all marketed benzodiazepines, there is standard language contraindicating the use of these drugs in pregnant women, based on two concerns: earlier data have suggested an increased risk of teratogenicity; and, there have been reports of CNS depression and also withdrawal phenomena in neonates of mothers who had received benzodiazepines prior to delivery. The sponsor has not addressed either issue in Contraindications or Warnings In fact, there is now a question regarding the teratogenicity of benzodiazepines, and this issue is currently being evaluated by the Division of Epidemiology and Surveillance. However, there appears to be no question about the potential for CNS depression and withdrawal in neonates. While zolpidem structurally is not a benzodiazepine, its pharmacology is so similar that I think it should be treated the same way as benzodiazepines with regard to this issue. Consequently, until the teratogenicity isssue is resolved and we can recommend changes for all benzodiazepines, I recommend that the two standard paragraphs be included in the Contraindications section for this drug. Therefore, we should ask the sponsor to include these two paragraphs in the Contraindications, as follows:

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

Ambien is contraindicated in pregnant women. If there is a likelihood of the patient becoming pregnant while receiving Ambien, 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."

5.3.4 Warnings

The sponsor has proposed Warnings statements about engaging in complex activities and about possible interactions with other CNS depressants. However, they have not included any statement about the potential for amnesia and certain behavioral adverse effects of the type seen with sedative/hypnotic drugs, nor have they emphasized the possibility that insomnia may be a symptom of some underlying psychicatric or physical disorder. We have recently strengthened the labeling for marketed benzodiazepine hypnotics in this regard, and I think that these added warnings would be entirely appropriate for zolpidem as well. I propose the following Warnings statement to replace that proposed by Lorex:

"Sleep disturbance may be the presenting manifestation of a physical and/or psychiatric disorder. Consequently, a decision to intiate 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 Ambien.

Because some of the important adverse effects of Ambien 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 benzodiazepines, a

class of drugs pharmacologically similar to Ambien. 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 are 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.

Ambien, like other sedative/hypnotic drugs, has CNS-depressant effects. For this reason, patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness or motor coordination such as operating machinery or driving a motor vehicle after ingesting the drug, including potential impairment of the performance of such activities that may occur the day following ingestion of Ambien. Patients should also be cautioned about possible combined effects with alcohol and other CNS-depressant drugs, and dosage adjustments may be necessary when Ambien is administered with such agents because of the potentially additive effects.

As with all sedative/hypnotic drugs, amnesia may be expected to occur unpredictably.

There have been reports of withdrawal signs and symptoms of the type associated with withdrawal from CNS depressant drugs following the rapid decrease or the abrupt discontinuation of benzodiazepines, a class of drugs similar in pharmacology to zolpidem (see DRUG ABUSE AND DEPENDENCE)."

5.3.5 Precautions

General

The sponsor has proposed comments regarding use in the elderly and debilitated, in systemic illness, and in depression. However, I find their language overly reassuring, and I have proposed the following alternative language:

"Use in the Elderly and/or Debilitated Patients- Impaired motor and/or cognitive performance due either to accumulation of drug after repeated exposure or unusual sensitivity to sedative/hypnotic drugs is a concern in the treatment of elderly and/or debilitated patients with drugs in this class. Therefore, it is recommended

that Ambien treatment be initiated with 5 mg in such patients (see DOSAGE AND ADMINISTRATION) to decrease the possibility of side effects, and they should be closely monitored.

Use in Patients With Concomitant Illness- Clinical experience with Ambien in patients with concomitant systemic illness is limited. Caution is advisable in using Ambien in patients with diseases or conditions that could affect metabolism or hemodynamic responses. Although preliminary studies did not reveal respiratory depressant effects at hypnotic doses of Ambien in normals, precautions should be observed if Ambien is prescribed to patients with compromised respiratory function, since drugs in this class have the capacity to depress respiratory drive. Since there are insufficient data from studies of Ambien in subjects with impaired renal function to conclude anything about the safety of Ambien in this population, Ambien should be used with caution in patients with renal impairment. A study in subjects with hepatic impairment did reveal prolonged elimination in this group, and therefore, treatment should be initiated with 5 mg in patients with hepatic compromise, and they should be closely monitored.

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

Information for Patients

I have prepared a modification of the Patient Package Insert (PPI) recently introduced for the marketed benzodiazepine hypnotics for use with Ambien. Consequently, this subsection should simply refer to the PPI that will need to appear as an attachment to the physician's package insert.

Drug Interactions

The sponsor has proposed a Drug Interactions subsection. However, I think it needs to be better organized and needs some additional material. Therefore, I have proposed the following alternative:

"CNS Active Drugs- A study involving haloperidol and zolpidem revealed no effect of haloperidol on the pharmacokinetics or pharmacodynamics of zolpidem. Imipramine in combination with zolpidem produced no pharmacokinetic interaction other than a 20% decrease in peak levels of imipramine, but there was an additive effect of decreased alertness. Similarly, chlorpromazine in combination with zolpidem produced no pharmacokinetic interaction, but there was an additive effect of decreased alertness and psychomotor performance. A preliminary alcohol interaction study

revealed no greater effect on psychomotor performance of the zolpidem/alcohol combination than zolpidem by itself.

Since the systematic evaluations of zolpidem in combination with other CNS active drugs have been limited, careful consideration should be given to the pharmacology of any CNS active drugs to be used with zolpidem. Any drug with CNS depressant effects could potentially enhance the CNS depressant effects of zolpidem.

Other Drugs- A study involving cimetidine/zolpidem and ranitidine/zolpidem combinations revealed no effect of either drug on the pharmacokinetics or pharmacodynamics of zolpidem.

Labor and Delivery

The sponsor has not proposed a 'labor and delivery' subsection. Since Ambien has no established use in this situation, I think a comment about this is needed, and I propose the following standard language for this subsection:

"Ambien has no established use in labor and delivery."

Nursing Mothers

Since we do not know the effects of zolpidem on the developing infant, I think a stronger statement is needed in this section, i.e., a recommendation against the use of this drug in nursing mothers. I propose the following alternative to this section:

"Studies in lactating mothers indicate that the half-life of zolpidem is similar to that in young normal volunteers (2.6 ± 0.3 hours). Between 0.004 and 0.019% of the total administered dose is excreted into milk, but the effect of zolpidem on the infant is unknown. The use of Ambien in nursing mothers is not recommended."

Geriatric Use

Since the use of zolpidem in the elderly is addressed above under 'General' information, there is no need to have a separate statement about appropriate caution about such use here.

5.3.6 Adverse Reactions

In an earlier section of this review (5.2.3.5), I have proposed language to be used for this section of labeling.

5.3.7 Drug Abuse and Dependence

Controlled Substance

While Drug Abuse Staff have recommended that zolpidem be classified as a Schedule IV controlled substance, this classification still needs to be

approved by NIDA. Therefore, this subsection should simply state that Ambien is not yet scheduled:

> "Ambien tablets have not yet been scheduled."

Abuse and Dependence

The sponsor has proposed a relatively weak statement that acknowledges a finding from abuse potential studies of an acute effect similar to diazepam, yet does not discuss at all the potential for physiological dependence. While it is true that the limited clinical trials experience with zolpidem does not reveal much evidence for a withdrawal syndrome, other than a suggestion of rebound insomnia, that experience is in fact too limited to use as a basis for coming to any definitive conclusion about dependence potential. Given the pharmacology of this drug, I think it is likely that, with additional experience, it will become apparent that zolpidem is like other sedative hypnotics in having a potential for inducing physiological dependence. Until more definitive data are available, I think it would be prudent to describe in this section what is seen with other drugs in the closely related benzodiazepine class. Therefore, I propose the following modification of the standard language in benzodiazepine labeling for this subsection:

> "Studies of abuse potential in former drug abusers found that the effects of single doses of zolpidem 40 mg were similar to diazepam 20 mg, while zolpidem 10 was difficult to distinguish from placebo on these measures.
>
> While the limited clinical trials experience for zolpidem circa 1991 does not reveal any clear evidence for a withdrawal syndrome, the similarity in the pharmacology of zolpidem and the benzodiazepine class of drugs suggests that zolpidem may have a potential for inducing physiological dependence similar to that seen for benzodiazepines. 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. 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 drugs in the benzodiazepine class, a proportion of patients taking these drugs 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. There is some evidence to suggest that gradual reduction of dosage will attenuate or eliminate some withdrawal phenomena. In most instances, withdrawal phenomena are relatively mild and transient: however, life-threatening events (e.g., seizures, delirium, etc.) have been reported.

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

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

5.3.8 Overdosage

The sponsor's proposed Overdosage section was generally acceptable. However, I have made several small modifications, as follows:

"Signs and Symptoms- In European post-marketing reports of overdose with zolpidem alone, impairment of consciousness has ranged from somnolence to light coma. There was one case each of cardiovascular and respiratory compromise. Individuals have fully recovered from zolpidem overdoses up to 400 mg. Overdose cases involving multiple CNS depressant agents, including zolpidem, have resulted in more severe symptomology, including fatal outcomes.

Recommended Treatment- General symptomatic and supportive measures should be used along with immediate gastric lavage where appropriate. Intravenous fluids should be administered as needed. As in all cases of drug overdose, respiration, pulse, blood pressure, and other appropriate signs should be monitored and general supportive measures employed. Hypotension and CNS depression should be monitored and treated by appropriate medical intervention. Sedating drugs should be withheld following zolpidem overdosage, even if excitation occurs.

The value of dialysis in the treatment of overdosage has not been determined, although hemodialysis studies in patients with renal failure receiving therapeutic doses have demonstrated that zolpidem is not dialyzable.

Poison Control Center- As with the management of all overdosage, the possibility of multiple drug ingestion should be considered. The physician may wish to consider contacting a Poison Control Center for up-to-date information on the management of hypnotic drug product overdosage.

5.3.9 Dosage and Administration

I generally agree with the content of the sponsor's proposed Dosage and Administration section, and I have made only minor revisions:

"The dose of Ambien should be individualized to maximize the beneficial effects.

The recommended dose for adults is 10 mg immediately before bedtime.

Downward dosage adjustment may be necessary when Ambien is administered with agents having known CNS depressant effects because of the potentially additive effects.

Elderly and/or debilitated patients and patients with hepatic insufficiency may be especially sensitive to the effects of Ambien. An initial 5 mg dose is recommended in these patients (see PRECAUTIONS).

The total Ambien dose should not exceed 10 mg."

6.0 WORLD LITERATURE

Dr. Collins, the clinical reviewer has indicated that the only published reports on this drug involve studies already fully reported in the NDA. We will ask for a literature update in the approvable letter.

7.0 FOREIGN REGULATORY ACTIONS

As of this time, I am aware of zolpidem being marketed in France, Belgium, Italy, Denmark, and Luxembourg; to my knowledge, it is approved, but not marketed in Greece, the Netherlands, Switzerland, and Germany. We will ask for an update on the regulatory status of zolpidem in the approvable letter.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE MEETING

We did not take zolpidem to the PDAC.

9.0 DSI INSPECTIONS

To my knowledge, DSI has completed inspections of three investigators (all satisfactory), i.e., Roth, Walsh, and Lahmeyer, and a fourth is pending on Leppik. All three critical trials, i.e., LSH 08, 17, and 19, are represented by the three completed inspections.

10.0 LABELING AND SBA

I have included draft labeling, a draft PPI, and a draft SBA as part of the approvable package. The clinical sections of labeling and the SBA needed almost total rewriting in order to adequately and accurately represent the clinical data in the application.

11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that the sponsor has provided substantial evidence for the safety and effectiveness of zolpidem as an hypnotic, and I recommend that the application is approvable, with the attached labeling and PPI. A number of additional requirements that need to be addressed prior to approval, or in some cases, subsequent to approval, have been detailed in the draft approvable letter.

cc:
Orig NDA 19-908
HFD-120
HFD-120/TLaughren/PLeber/DCollins
HFD-100/RTemple

DOC: ZOLPMEM.5

HFD-120

Review and evaluation of clinical data

NOV 15 1991

NDA	19-908
Sponsor	Lorex
Drug	AMBIEN (Zolpidem tartrate)
Drug class	1-C
Proposed indications	Sedative/hypnotic
Material reviewed	"Zolpidem safety summary: European post-marketing safety data"
Date of correspondence	June 28, 1991
Date received	July 2, 1991
Safety review date	n/a

Background Zolpidem was first marketed in France in February, 1988; registration has also been accomplished in Belgium (April 1989), Italy (Jan 1990), Denmark (Jan 1990), and Switzerland (Sept 1990). This submission is the sponsor's summary of the first 885 reports of adverse drug events (ADEs) defined according to FDA criteria and collected between February, 1988, and December, 1990. While not submitted as part of the pending NDA, the data are relevant to an evaluation of the clinical safety of zolpidem, and are being reviewed as an Addendum to the Application.

Basic pharmacology Zolpidem is an imidazopyridine compound, structurally unrelated to other available hypnotics. It acts via selective binding to the omega-1 receptor, which is part of the $GABA_A$ macromolecular complex. Recommended starting dose is 10 mg at hs; starting dose in the elderly is 5 mg.

Clinical experience The present report is based on 136.44×10^6 person-days of therapy, as follows:

- cont'd -

France	121.96 x 10^6 days of therapy
Belgium	3.46 " " "
Italy	10.61 " " "
Denmark	0.61 " " "

The data All clinical events collected through the sponsor's spontaneous reporting system were processed according to standardized methods and included in the present report, irrespective of the source or causality assessment. The distribution of ADEs is as follows:

	Notifications	Exclusions	Non-MSI	MSI
France	836	14	317	505
Belgium	21	3	5	13
Italy	22	-	1	21
Denmark	6	-	-	6
	885	17	323	545

Exclusions: a) reports which were subsequently the subject of a publication; b) events occurring in Phase 4 clinical trials; c) questions relative to the safety of the drug which were mistaken for adverse events; and d) duplicates.

MSI = Minimum Standard of Information, ie, an identifiable source; a patient; a suspect drug; a suspect reaction. Serious events not fulfilling MSI criteria are listed, but are not included in analyses or calculations of rates.

Since 95% of the events originated in France, the analyses are focused on those data. Of the 505 French reports which fulfilled MSI criteria, 11 were determined not to be ADEs. The distribution of the remaining 494 ADEs was as follows:

	1988	1989	1990	Total
Professional practice	94	209	126	429
Overdose	26	19	8	53
Suspicion of drug abuse	-	1	1	2
Suspicion of withdrawal	1	2	2	5
Lack of expected pharmacological action	-	4	1	5

Of ADEs reported by a physician, 344/429 ADEs were CNS-related; 85/429 were non-CNS.

Rates for the principal CNS-related ADEs reported by physicians, calculated with respect to the number of days of therapy, were as follows:

- cont'd -

Days of therapy (x 10^6)	1988 17.1	1989 42.0	1990 62.8	Total 121.9
Confusion	0.64	1.0	0.43	0.67
Vertigo/dizziness	0.88	0.43	0.14	0.34
Perceptual disturbances	0.35	0.28	0.33	0.32
Agitation	0.41	0.43	0.16	0.28
Memory disorders	0.05	0.43	0.16	0.24
Nightmares	0.4	0.36	0.05	0.20
Daytime drowsiness	0.29	0.31	0.05	0.17
Somnabulism	0.17	0.14	0.06	0.11
Headache	0.34	0.14	0.03	0.11
Insomnia	0.34	0.09	0.05	0.11

It is of interest that memory disorder is the only ADE with a higher incidence in 1990 than in the year of launch; the 1990 rate (0.16 events/10^6 patients days of therapy) is well below 1989's 0.43 rate. Events reported as memory disorders were generally described as transient; none involved inappropriate behavior; and none was regarded as having pathological significance.

The principal non-CNS events in the French experience were:

	1988	1989	1990	Total
nausea	1	2	-	3
vomiting	2	4	-	6
abdominal pain	3	2	1	6
diarrhea	-	2	1	3
mouth dry	1	2	1	4
dyspepsia	2	-	1	3
hiccup	-	-	1	1
taste perversion	-	2	-	2

The Belgian, Italian, and Danish data are similar to the French experience.

The sponsor's conclusions:

> 1. The adverse event profile of zolpidem reflects the pharmacological properties of the drug. It is consistent with the European registration file safety data.
>
> 2. No serious and unexpected adverse events were identified for which a relationship to zolpidem could be established. In particular there were no cases of drug abuse or withdrawal effects.

- cont'd -

3. No previously unrecognized risk factors were identified.

4. These results do not warrant any changes in product labelling.

Discussion The data are similar to those reported in the NDA, both as to the character of the adverse experiences with zolpidem and their relative frequencies.

Recommendations Concur in the sponsor's judgment, ie, no change in labelling is warranted.

David M Collins, MD

cc:IND
HFD-120
HFD-120/Laughren
/Mille
/Collins
ft/dmc/July 9, 1991

HFD-120

REVIEW AND EVALUATION OF CLINICAL DATA

NOV 15 1991

NDA 19-908

Sponsor: Lorex

Drug: zolpidem

Dates of Submission: January 26, 1989; February 12, 1990

The sponsor has submitted a large number of studies that examine special aspects of zolpidem, e.g., daytime alertness, residual effects, rebound insomnia and memory which do not have a direct bearing on efficacy.

The sponsor categorized the studies according to topic and identified the principal studies for each topic. The definition of a principal study varied from topic to topic with the exception that they all were required to be double-blind and placebo controlled. In the case of daytime alertness, all five studies using the Multiple Sleep Latency Test (MSLT) were included.

The topics, numbers of studies and principal studies were as follows:

(1) Daytime Alertness (MSLT): 5 studies
(2) Residual Effects (Psychometric Studies): 22 studies; 7 principal studies.
(3) Subject Ratings of Alertness
(4) Daytime Alertness (Rating Scales): 4 studies
(5) Rebound Insomnia: 17 studies; 4 principal studies.
(6) Memory: 11 studies; 3 principal studies.
(7) Studies of Drug Interactions: 6 studies
(8) Drug Abuse Potential: 2 studies

In the following, I will describe the principal studies for each topic. In the drug interaction studies, only the studies with behavioral or psychometric data will be discussed. My discussion of the studies will include a brief description of the design, the test variables and the results.

A. Daytime Alertness:

Of the five studies in this category, four had zolpidem administered at bedtime and the subjects slept in the sleep laboratory with a constant length of time allowed in bed. The MSLT was carried out for 20 minutes at 2 hour intervals five times during the next day. The outcome measure was the number of minutes to fall asleep with a maximum

opportunity of 20 minutes at each testing. The fifth study involved afternoon drug administration with evening sleep latency tests.

The studies included in this category were:

1. LSHII/SCHARF
2. Ruther/IGEOI
3. Simon/IFR29/35
4. Terzano/IIT02
5. Nicholson/IGB02/08

1. In the Scharf study, there were two independent crossover regimens, the first,(17 subjects), comparing PL, Z-5mg and Z-15mg: the second (16 subjects) comparing PL, Z-10mg, Z-20mg. The subjects were normal elderly volunteers. Each drug administration consisted of 2 nights of each dose with the MSLT following the second night. There was a washout of at least 4 nights between each treatment.

The analyses compared the zolpidem dosages to placebo at each time period. No differences were found among the treatments for either crossover.

2. In the Ruther study, 10 adult male volunteers received single doses of five different treatments (placebo, zolpidem l0mg, zolpidem 20mg, triazolam 0.5mg and lormetazepam 1mg) following a crossover design. A washout period of 5 days separated each treatment. Subjects spent 2 nights in the sleep lab: placebo was administered the first night and one of the experimental treatments, the second night. The MSLT was administered five times on the day following the second night.

The mean sleep latencies ranged from 10-20 minutes and ANOVAs among treatments at each time interval were not significant. The proportion of patients who fell asleep differed significantly across treatments. Of a total of 50 opportunities (5 doses X l0 subjects), the volunteers fell asleep 23 times after triazolam, 25 times after placebo, 29 times after zolpidem 20mg, 32 times after l0mg zolpidem and 34 times after lormetazepam. The difference between triazolam and lormetazepam was significant.

3. In the Simon study, 12 normal adult males were given single doses of zolpidem 20mg, flunitrazepam 2mg and placebo following a crossover design with a one week washout between each treatment. Five MSLT's were carried out during the day following the drug administration. The Friedman Rank Test was significant reflecting the least daytime sleepiness with zolpidem and the most with flunitrazepam. Placebo was intermediate.

4. In the Terzano study, single nighttime doses of zolpidem l0mg and placebo were paired with the presence or absence of acoustic disturbance during sleep time in 12 healthy volunteers. It was partially double-blind in that it was not possible to blind the acoustic disturbance. The MSLT (5 tests) was conducted the next day.

There were no significant differences between treatments at 10:00 A.M., 12:00, and 6:00 P.M. The differences were significant at 2:00 and 4:00 P.M. with longer sleep latencies (greater alertness) on zolpidem than placebo. There was no effect of the presence or absence of noise during the night on the MSLT scores.

5. Nicholson carried out a crossover comparison in 6 male volunteers of single doses of *Zolpidem l0, 20, 30mg, diazepam l0mg and placebo on alertness.* Each treatment was administered at 2:00 P.M. (one week washout between treatments) and alertness was tested 6.5, 7.5, 8.5 hours after drug administration. None of the treatment comparisons were significant.

Summary:

The Multiple Sleep Latency Test is objective and has been shown to reliably identify daytime drowsiness with the sedative antihistamines and on the day following administration of some hypnotics. The main validation for this test has been the similarity of results with it to verbal reports of drowsiness. The results of the above studies would suggest that zolpidem does not produce daytime drowsiness.

In the proposed labeling, the sponsor states "From the results of objective measures of daytime drowsiness, [psychomotor performance tests and patient ratings of alertness], there were no indications of residual (carry-over) effects after bedtime administration." These five studies would support the "objective measures" section of the labeling.

B. Psychomotor Tests of Residual Effects:

As stated above, the submission contains 22 studies using psychomotor tests to assess residual effects of the drug on the day following nighttime drug administration. The sponsor identified seven studies as principal: double-blind, placebo controlled, used psychomotor tests known to be sensitive to residual effects of hypnotics, and had an adequate sample size for analysis. In addition, drug administration was in the evening and subjects slept in a controlled environment with time in bed fixed.

The tests which were selected as most appropriate were the Digit Symbol Substitution Test (DSST) where the numbers one to nine are paired with a simple symbol. The tester is asked to fill in the boxes with the numbers given but without the symbol. The code is available for reference throughout. The test is timed and the score is the number correct.

Another test was the Symbol Copying Test. Here, the subject is asked to copy the symbol from the box above to the empty box below. The test is timed and the score is the number completed correctly.

The third test is simple reaction time (how long it takes to respond to a signal) and the fourth, complex (or choice) reaction time. Here the subject is asked to respond only if a specified condition exists prior to the presentation of the signal.

The principal studies were:

1. Simon/IFR29/35;
2. Grilliat/IFR22;
3. LSH02/Roth;
4. LSHII/Scharf;
5. LSH08/Roth, Vogel;
6. LSH09/Walsh;
7. LSH17/Roth,Scharf,Vogel,Walsh.

1. 1FR29/35/Simon. This study was described under daytime alertness (single dose comparison of nighttime administration of zolpidem 20mg, flunitrazepam 2mg, and placebo). The psychomotor tests in this study were carried out following a standard breakfast on the morning after the nighttime dose. The tests were the DSST, a Choice Reaction Time (CRT) and the Critical Flicker Fusion Test (CFF). The analyses for treatment effect were significant for each of these tests. In all cases, flunitrazepam was significantly worse than placebo and worse than zolpidem while there was no difference between zolpidem and placebo.

2. 1FR22/Grilliat used a double-blind, single dose, crossover, comparison of zolpidem 20mg, triazolam 0.5mg, and placebo with a one week washout between each treatment in 9 normal volunteers. Drug administration was in the evening and testing in the following morning. The tests included simulated driving, a coded test similar to DSST, an auditory and visual reaction time test and a proofreading test. The only significant treatment difference was for the driving test with more errors for triazolam than zolpidem. There was no difference between zolpidem and placebo or triazolam and placebo.

3. LSH02/Roth compared placebo and zolpidem 2.5, 5, 7.5, 10, and 20mg following a crossover design in 12 normal male volunteers. Each treatment was administered in the evening on two consecutive days followed by one night of placebo with a washout of at least 3 days between treatments. The subjects completed the DSST, SCT, SRT, and CRT tests on the mornings following the evening administrations.

There was a significant difference among the 6 treatments on the simple reaction time with the placebo & Z-20 comparison on the second night showing Z-20 was slower than placebo. None of the other tests showed any effect.

4. LSH11/Scharf. This study was described in the daytime alertness section (compared Z-5, 10, 15, 20mg and placebo in 33 elderly volunteers in 2 independent crossovers). The DSST was completed before bedtime (20min post-dosing) and in the A.M. There was a significant difference between zolpidem and placebo with lower (worse) scores for Z-5, 10, 15 and 20mg in the morning following the second dosing night.

5. LSH Roth, Vogel in a single dose, parallel group design, compared Z-5, 7.5, 10, 15, 20mg and placebo in 462 normal adult volunteers. The design used the first night in a sleep lab as a model of insomnia. The emphasis was placed on the placebo, 7.5mg and l0mg zolpidem groups with l00 subjects in each group. The drug was administered in the evening in the sleep laboratory and psychometric testing (DSST, SCT) was carried out in the morning. Neither the DSST or the SCT showed any difference between placebo and the two zolpidem doses.

6. LS1T Walsh studied zolpidem 5, 10, 15, 20mg and placebo following a crossover design on insomnia produced by a 3 hour phase advance. 31 normal adult volunteers were the subjects and were tested in one of two independent crossovers. Each treatment consisted of two consecutive nights with placebo given the first night at the subject's usual bedtime. On the second night, the bedtime and drug administration were advanced 3h compared to night one. The DSST and SCT were completed in the morning following night one and night two. There was no overall treatment effect for either night or crossover.

7. LSH '/Roth,Scarf,Vogel,Walsh carried out a parallel group comparison of placebo, zolpidem l0mg and zolpidem 15mg in 75 adults with insomnia. The study began with a one week placebo lead-in followed by a 5 week experimental treatment phase. Patients had PSG on the first two days of each of the six weeks and DSST was completed each morning following a night spent in the laboratory. None of the overall analyses of the DSST and SCT weekly scores were not significant suggesting no difference between treatments on the test.

Summary:

Of the seven studies, five showed no effect of zolpidem on next day testing on psychometric tests. One of the five studies included flunitrazepam and this was found to affect performance. Of the remaining two studies, one found Z - 20mg reduced the reaction time in comparison with placebo. The seventh study found DSST was reduced in an elderly population by all doses of zolpidem on the day after two nights of dosing.

Perhaps the labeling should indicate that the elderly may be more susceptible to residual effects.

C. Subject Ratings Of Alertness

A comprehensive listing of studies including patient ratings was not available. However, when reviewing the principal studies above, I noted occasionally that daytime alertness/drowsiness had been evaluated with a visual analogue scale (VAS) and the results of these ratings are given below.

Ruther used the Stanford Sleep Scale and other VAS and the report indicated that the short acting hypnotics did not show daytime residual effects (no difference between placebo, zolpidem or triazolam).

Simon used a VAS to assess vigilance and mood the following morning. The results showed no difference between zolpidem and placebo although they were different from flunitrazepam which decreased vigilance.

Terzano used a VAS with each MSLT to determine how sleepy or awake the subject felt. Neither drug (zolpidem or placebo) nor noise (present or absent) affected the VAS scores.

LSH /Roth, Vogel used the VAS to assess daytime sleepiness and there were no significant differences between the zolpidem doses and placebo.

Summary:

The patient ratings appear to support the MSLT in that zolpidem does not appear to produce residual effects of drowsiness. It also supports the labeling statement concerning daytime patient ratings of alertness.

D. Rebound Insomnia

Principal trials were required to be double-blind, placebo controlled and have had post-treatment nights with a separate analysis of the first post-treatment night. The following were identified as principal trials by the sponsor:

1. LSH02/Roth
2. LSH11/Scharf
3. LSH /Roth, Scharf, Vogel, Walsh
4. LSH /Cohn, Dochery, Fillingim, Kann, Lahmeyer, Leppik

1. LSH02/Roth. This study is described in B-2 above. The treatments were Z - 2.5, 5, 7.5, 10, 20mg and placebo and the subjects were 24 adult volunteers. Each treatment was administered for two nights and double-blind placebo was given on the third night to test for rebound phenomena. There was no difference among doses for the sleep variables on the third night. On the PSG, there was less Stage 3-4 for the Z-5 and Z-20mg group and there was a slight increase in REM for all doses of Z-5mg and above.

2. LSH11/Scharf. This study was described in A-1 and B-4 above (Z - 5, l0, 15, 20mg and placebo in 33 elderly volunteers in two independent crossovers). Rebound insomnia was measured during one night of placebo following two consecutive nights of zolpidem/placebo administration.

Significant PSG findings on night 3:

(a) Sleep efficiency decreased for Z-15mg over placebo.
(b) No. of awakenings increased for Z-10 and Z- 20mg over placebo.
(c) In the Z - 15mg group, there was an increase in % Stage 2 sleep. The Z - 15mg group also showed a decrease in % of REM in crossover 1. In the Z - 10 and Z-20mg group, there was an increase in % Stage 1 sleep.

Questionnaires elicited somewhat more dissatisfaction with sleep on the morning following the placebo night as detailed in the following:

Z-15mg - significantly shorter latency than placebo
Z-15, 20mg - significantly more awakenings than placebo
Z-10, 15, 20mg - significantly poorer quality of sleep than placebo
Z-10, 15, 20mg - significantly less ease to sleep than placebo
Z-10, 15, 20mg - significantly less refreshing sleep than placebo

3. LSH /Roth, Scharf, Vogel, Walsh. This study was described under B-7 above (Z - 10, 15mg, and placebo in 75 adult insomniacs). Rebound was assessed during three placebo post-treatment nights which followed 5 weeks of treatment. The results are given below. The between treatment analyses are described first and are followed by the change from baseline analyses.

(a) PSG. The only significant finding was for night 1 of the post treatment phase. In the Mean Wake Time during sleep, the Z-15mg group spent more time awake than placebo.

(b) Questionnaires showed that the analysis of sleep quality was significant on the first post-treatment night with the Z - 15 mg group recording poorer quality of sleep than the placebo group. On an analogue scale, the Z-15mg subjects were significantly more sleepy than placebo on the morning after the first placebo night.

In the change from baseline to post-treatment night analyses, there was a significant difference on the first post-treatment night in latency with a longer latency for the Z - 10mg group compared with placebo.

4. LSH /Cohen, Docherty, Fillingim, Kann, Lahmeyer, Leppik. This study which followed a double-blind, placebo controlled, parallel group design compared zolpidem l0mg, zolpidem l5mg and placebo in 145 adult outpatients with chronic insomnia. The study duration was 31 nights preceded by a 3 day pre-trial and 4 day post-trial placebc segment. No polysomnography was carried out.

The rebound effects were assessed by questionnaires during the single blind 4 day post-trial placebo segment. The only significant effects were as follows:

- Compared with the initial placebo baseline, Total Sleep Time (TST) was significantly shorter in the 15mg group than in the placebo and 10mg groups (where TST increased).
- Morning sleepiness was significant for post days l, 2, and 3 with the 15mg group showing more sleepiness than the placebo group.

Summary:

Overall, although the findings are scattered and not necessarily dose dependent, it does appear that there are posttreatment effects following discontinuation of zolpidem. These findings were more consistent on the questionnaires than with the PSG. In one study or another almost all facets of sleep were ultimately affected although they seemed to be limited primarily to the first night post dose.

In the proposed labeling the sponsor stated that "There was no polysomnographic evidence of rebound insomnia at recommended doses". This should be amended to indicate there was subjective evidence of post-treatment effects.

E. Memory

The principal memory trials (double-blind, placebo controlled, and adequate sample size) were:

(1) LSH11/Scharf

(2) Simon/IFR29/35
(3) Grilliat/IFR22

All of these studies were described in the psychometric test section. The studies evaluated aspects of retrograde amnesia, anterograde amnesia and short term memory.

(1) LSH11/Scharf. This study is described above under A-1 (35 normal elderly, 2 nights active - Z 5, 10, 15, 20mg or placebo - and the third night placebo). Memory testing consisted of the Bushke Memory Test 20 minutes after dosing, with recall just before bedtime and in A.M. An alternate list from the Bushke was also presented in the A.M. following the first list with recall 10 minutes later. There was only one significant analysis, namely, reduced recall of the second list in the morning after the second night for the Z - 15mg condition compared with placebo.

(2) Simon/IFR29/35 (See A-3 above) compared single doses of placebo, zolpidem 20mg and flunitrazepam 2mg in 12 normal adult males. In the morning following nighttime drug administration, two memory tests were given. One was a paired associate learning test with immediate recall and the other required the retention of 12 pictures for 30min after presentation. This second test was not described in any further detail in the report except that two scores were collected, one unprompted recall and one prompted.

There were numerous significant results, all arising from the poorer performance when on flunitrazepam in comparison with placebo and zolpidem. There were no significant differences between zolpidem and placebo.

(3) Grilliat/IFR22 (See B-2 above) compared single doses of zolpidem 20mg, triazolam 0.5mg and placebo in 9 normal adults. The drugs were administered in the evening and the memory testing was done in the morning. The memory tests consisted of digit span (putative immediate memory) and two "long-term" memory tests. One used a 24 word (nouns) list which the subject read for 5 minutes in the evening and recalled in the morning. He was then allowed to complete his recall by picking missing words from a list of 48 words. The second required remembering a time table presented in the evening with recall in the A.M. There was also a test to evaluate the drugs' effects on learning by having the subject receive a phone call 30 minutes after drug administration the content of which was to be recalled in the A.M. They also administered a test like the time table after other tests were completed in A.M. with recall at noon.

The results of the ANOVA for each test across the three treatments were uniformly nonsignificant.

Summary:

There was little evidence of impaired learning ability or impaired memory in the studies above. However, the number of subjects was very small and the evaluations were not

systematic. In one of the drug interaction studies (Coupez) which evaluated whether or not an interaction existed between zolpidem and imipramine, the investigator reported that anterograde amnesia occurred in 5 of 6 subjects who received the combination and in one on zolpidem alone. In one of the drug abuse studies, both zolpidem and triazolam produced poorer scores on a short term memory test (Enter and Recall). There was also impairment on a 'long term' memory test (Picture Recall and Recognition) for both drugs although triazolam produced significantly more impairment than zolpidem on the immediate and delayed recall. Also higher doses tended to produce more impairment (see Drug Abuse Section - Griffiths study).

There is a statement in the labeling that memory in the elderly was not affected by the bedtime administration of recommended doses of zolpidem which probably refers to the Scharf study above. The labeling also goes on to say that two studies of zolpidem in young adults, there was no effect of zolpidem on memory. It is my opinion that the anecdotal information provides some evidence that memory is impaired following zolpidem administration although this may occur at doses higher than recommended in the package insert.

F. Drug Interactions

There were ten studies of interactions between Zolpidem and alcohol, caffeine, imipramine, chlorpromazine, haloperidol, cimetidine/ranitidine, warfarin, digoxin and R0 15-1788. In the following, I will describe briefly the studies which include behavioral or psychometric measures, i.e., the studies on alcohol, caffeine, imipramine, chlorpromazine and haloperidol. The remaining interaction studies were primarily pharmacokinetic and presumably will be covered in the Biopharmaceutics review.

I. Coupez/1BE04 - Alcohol

Twelve adult male volunteers participated in this double-blind, 6 period crossover comparison of zolpidem 20mg, triazolam 0.5mg and placebo each administered twice, once with alcohol in juice and once with juice alone. The alcohol dose was 1.5ml of 40% vodka (0.6ml alcohol) per kg. The treatments were administered in the A.M. The alcohol (or juice alone) was administered one hour after the study drug. Treatments were separated by an eight day washout period. The tests which were given 30 minutes post alcohol/orange juice administration were: Proofreading test, Stroop test, Tapping test, Bead stringing, Memory - recall 8 playing cards. Visual Analogue Scales (VAS) were also used.

The results for the VAS for Vigilance (Drowsiness) indicated that alcohol had no effect while zolpidem and triazolam both reduced vigilance in comparison with placebo. There was no interaction between alcohol and the treatments.

The same pattern was found for all the psychometric analyses, that is, no alcohol effect and no interaction. There were significant treatment effects which reflected a difference between placebo and the two active drugs, zolpidem and triazolam. In most cases, both drugs has poorer scores although in some cases, there were reduced scores in only one or the other drug. (The description of the statistics was not overly clear.)

The PK studies also found alcohol had no effects on plasma concentrations of zolpidem or triazolam.

2. Thebault - Alcohol

Twelve healthy male volunteers participated in this double-blind 6 period crossover of zolpidem 20mg, flunitrazepam 2mg and placebo each administered twice, once with and once without alcohol. The amount of alcohol was 6.5ml of wine per Kg. The drugs were administered in the evening, the alcohol with supper prior to the drugs.

Evaluations which included VAS and psychometric tests were performed the following morning. The VAS focused on the quality of sleep etc. The psychometric tests included tests of visual and auditory reaction times, proofreading test, Stroop test, critical flicker fusion, and driving simulation.

The results of the VAS concerning the night's sleep suggested that zolpidem produced a more restful night than flunitrazepam. The analysis of the VAS concerning mid-morning liveliness, vigilance and general condition indicated there was no difference between zolpidem and placebo. The scores were significantly worse for flunitrazepam than placebo.

On the psychomotor tests, there was no difference between zolpidem and placebo. Two tests worsened with flunitrazepam (CFF and driving simulation). There was no effect of alcohol except for an increased error score on proofreading.

3. Vandel - Caffeine

This study evaluated possible pharmacodynamic interactions between the oral administration of zolpidem 20mg and caffeine 300mg in 8 adult volunteers following a single dose, double-blind crossover design. Zolpidem or placebo was administered in the evening 45 minutes after taking capsules of caffeine or placebo. The outcomes assessed were subjective measures of the quality of sleep immediately following zolpidem/placebo administration.

Following administration of caffeine and then placebo, insomnia was seen in 5 subjects out of 8. No insomnia occurred following administration of caffeine and zolpidem. Using

the Stanford Sleepiness Scale, caffeine administered prior to Zolpidem in the evening did not affect sleep latency.

4. Coupez - Imipramine

This study compared single doses of imipramine 75mg, Zolpidem 20mg and the combination which were administered to 6 male volunteers in the morning. Measures included self ratings (VAS) of vigilance and overall state of being taken before and after treatment, side effect reports and blood levels.

According to self reports, drowsiness occurred in all subjects with all treatments. It was mild following imipramine, mild to moderate following Zolpidem and mostly severe following the combination of Zolpidem and imipramine. Anterograde amnesia occurred mostly following the combination. Memory was not assessed systematically. Subjects spontaneously reported that they couldn't recall incidents following the combined administration.

The VAS which measured vigilance (alert vs drowsy) was not significant. However, reports of drowsiness increased with reports of mild drowsiness following imipramine, mild to moderate drowsiness following zolpidem and severe drowsiness following the combination. The PK variables were essentially unaffected except for the IMI C_{Max} which was decreased after zolpidem administration.

5. Harvengt/IBE03-Chlorpromazine

Single oral doses of zolpidem 20mg, chlorpromazine 50mg or their combination were administered in the morning following a crossover design to 6 normal (male/female) adult volunteers.

The PK results indicated there was no difference in the PK of zolpidem alone and in combination with chlorpromazine. The chlorpromazine levels were too close to the limit of sensitivity to model the kinetics so that the CPZ vs the combination could not be tested.

The assessments consisted of subjective measures including self report and the VAS, and objective tests (Manual Dexterity and the Stroop test). On the Manual Dexterity test, only the combination vs CPZ at 1 hour postdose was significant with the combination doing more poorly than CPZ. On the Stroop test, at 1 hour postdose the combination did more poorly than CPZ alone and at 3 hours post dose, the combination did more poorly than zolpidem alone. At 1 and 3 hours post dose, zolpidem did more poorly than CPZ. Subjects reported sedation on zolpidem and on the combination. CPZ alone had no

effect on VAS, Zolpidem decreased wakefulness and concentration and the combination increased the duration of both.

6. Lambert/IFR21-Haloperidol

Single doses of Zolpidem 20mg, haloperidol 2mg and their combination were administered in the morning following a crossover design to 6 healthy male volunteers.

The only assessments were VAS on drowsiness and overall clinical condition. Sedation was reported by all subjects in each treatment. Determined by a questionnaire, haloperidol and the drug combination produced more sedation than zolpidem alone. There were no treatment differences on the VAS.

Analysis of the PK measures did not show any effect of haloperidol on zolpidem blood level characteristics although because the haloperidol plasma levels were close to the limit of sensitivity, not all variables could be measured.

Summary:

The warnings section of the labeling states that 'although the combined effects of 20mg of STILNOX and the equivalent of 3 oz of ethanol have not been shown to be greater than the effects of Stilnox alone, patients should be cautioned against.....Under Drug Interactions, a similar statement is included as to the lack of effect of alcohol. There is also a statement that the effects of zolpidem and imipramine are additive as are the effects of zolpidem and chlorpromazine. These effects are for decreased alertness. It also states that zolpidem and chlorpromazine have an additive effect on psychomotor tests. These statements are supported by the study results. There are some problems with the studies. One is the very small number of subjects in these studies. Another is that a finding of no effect may not be valid for reasons of power etc. In the alcohol studies, only one dose of alcohol was used (per kg) and there was no alcohol effect on the tests except for one error score for either alcohol study.

G. Drug Abuse

There were two pilot and two studies submitted to the NDA which evaluated the abuse potential of Zolpidem. Both Protocol LSH13 which was a pilot dose finding study and LSH14, the major study, were included in the original submission. These two studies were carried out by D.R. Jasinski. Protocol LSH15, a pilot dose finding trial, was also submitted in the original submission. Protocol LSH16 was submitted in an amendment. Both LSH15 and LSH16 were conducted by Roland R. Griffiths. Both investigators worked at the Francis Scott Key Medical Center in Baltimore MD.

(1) LSH16/Griffiths compared zolpidem 15, 30, 45mg and triazolam 0.25, 0.5, 0.75mg and placebo using a double-blind crossover design in outpatient adult male volunteers with a history of sedative drug abuse. There were 9 experimental sessions with no washout between sessions. The first two sessions were for practice during which no capsules were administered. In subsequent sessions, baseline measures were taken at 9:30 A.M., drugs were administered at 10:00 A.M. and the session continued for six hours with two half hour and then hourly testing schedules.

The measures consisted of a Drug Effect Questionnaire, Subjective Effects Questionnaire, Addiction Research Center Inventory (ARCI), POMS, Next Day Questionnaire, Observer Rated Questionnaire, Psychomotor/Cognitive Performance Measures (circular lights, DSST, Balance Tasks, Reaction Time, Enter and Recall (eight digits), Picture Recall/Recognition).

Forty subjects were screened, 25 qualified and 7 who participated in practice sessions were discontinued for drug-positive urine samples or failure to appear for sessions. Three additional subjects were terminated for the trial for the same reasons. Fifteen completed the study.

There was a dose related effect on psychometric tests, and this effect was similar for triazolam and zolpidem for the most part. The report emphasized the fact both drugs underestimated the degree of impairment prior to the DSST which is a finding found in other benzodiazepines. Memory was adversely affected by both drugs (two highest triazolam doses and highest zolpidem dose) on the Enter and Recall Test (short term memory). The Picture Recall and Recognition test (long term memory) showed greater impairment with triazolam than zolpidem on the immediate and delayed recall. On the immediate recall, all doses of triazolam and the highest dose of zolpidem showed impairment. On the delayed recall, all doses of both drugs produced impairment. In the delayed recognition subtest, the two highest doses of triazolam and zolpidem produced impairment. It was also noted that while triazolam was uniformly perceived as a classic sedative hypnotic at the higher doses, with zolpidem, the higher doses produced a decreased number of classifications as sedative hypnotic which the sponsor felt might enhance liking for the drug. Both drugs produced increased ratings of drug effect, drug liking, and depressant effect although zolpidem also increased ratings of negative effects together with vomiting which the sponsor felt might attenuate the positive effects.

(2) LSH14/Jasinski compared zolpidem 10, 20 and 40mg, diazepam 10 and 20 mg and placebo using a six way crossover in 12 inpatient male volunteers with a history of substance abuse. The testings took place over six consecutive days with several days pretrial of screening etc. The assessments consisted of Subject Drug Rating Questionnaire, Subject Drug Identification Questionnaire, Subject Specific Drug Questionnaire, Addiction Research Center Inventory (ARCI), Observer Drug Rating Questionnaire, Observer Specific Drug Effect Questionnaire.

The results indicated the predominant profile of subjective effects produced by zolpidem were similar to that of diazepam. The doses that was considered equivalent were zolpidem 40mg and dizepam 20mg based on mean peak scores and 3 hour AUC's. Zolpidem was identified as a benzodiazepine and was equally effective to diazepam in liking etc. The results, however, were not identical. Zolpidem produced less sedation as indicated by the lack of identification as a barbiturate and lower scores on the sleepy scale compared to diazepam and higher scores on the full of energy scale. Zolpidem but not diazepam reported increased scores on the drunk, confused and do distances, colors or shapes appear changed items. Observers also reported many similarities and also reported less sleepy etc with zolpidem. They concluded that this similarity to diazepam may suggewt it would have an abuse potential of the diazepam type. The unique effects of zolpidem were not shown to be aversive relative to diazepam but the author hypothesized, may become so. Finally, zolpidem 10mg was only minimally psychotropic,

In the labeling, the Abuse and Dependence section states that studies of abuse potential in former drug abusers found that the effects of single doses of 40mg zolpidem were similar, but not identical, to 20 mg of diazepam and the effects of 10mg of zolpidem were close to, if not indistinguishable from, placebo. There were a multiplicity of measures in both drug abuse studies and it was not clear that this was taken into effect when the analyses were done.

J. Hillary Lee

J. Hillary Lee, Ph.D.

NDA 19-908
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NOV 15 1991

Review and evaluation of clinical data

NDA	19-908
Sponsor	Lorex Skokie, Illinois
Drug	AMBIEN (zolpidem tartrate)
Indication	Sedative/hypnotic
Drug class	1-C
Date received	Jan 30, 1989
Clinical reviewer	David M Collins, MD HFD-120

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Appendices

- cont'd -

1.0 Background

Zolpidem was developed by a French firm, , and was evaluated in a capsule formulation in trials in Europe, the UK, and S America. Lorex initiated clinical trials in the US with the same formulation in July 1985 under IND

Zolpidem has been marketed in France since 1988. At the time of submission of the NDA, registration was pending in the United Kingdom, Belgium, Luxembourg, Holland, West Germany, Spain, Italy, Switzerland, Greece, Denmark, Iceland, and Republic of Ireland. No adverse regulatory actions have been reported.

The following issues are critical to this review:

1. Chemistry

a) Route of synthesis has been changed since the original IND submission. The new method produces different impurities; total amount is no greater than that seen with the original method.

b) The new synthesis also results in a metholate polymer, the clinical significance of which is undetermined.

c) The film-coated tablet proposed for marketing may have delayed release properties, raising the question of bioavailability with the capsule used in pre-NDA studies.

2. Biopharmaceutics - In a preliminary review, the Division of Biopharmaceutics [HFD-420] has concluded that the film-coated tablet is not bioequivalent to the pre-NDA capsule. Three studies, begun after the submission of the NDA, address the bioavailability / bioequivalence issue.

LSH25/Hunt. Dose proportionality. Initiated 9/89. (N=45).
LSH27/Dixon. Rel bioavailability. Initiated 10/89. (N=30).
LSH28/Figueroa. Bioequivalence. Initiated 10/89. (N=45).

3. Environmental impact - The original Application does not contain an environmental impact statement.

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4. The Division of Scientific Investigations [HFD-340] has indicated [Young/File, Nov 21, 1989] that two centers participating in **LSH** (Roth and Walsh) and two in **LSH** (Lahmayer and Leppik) will be subjected to routine audit, ie, without cause.

2.0 Material Reviewed

The original NDA, submitted Jan 26, 1989, was received Feb 1, 1989, and consists of 361 volumes, numbered 1.1-1.361. The following Amendments have been received:

Feb 12, 1990 - (1) **LSH15/Griffiths:** Abuse Potential Evaluation of Zolpidem in Outpatient Subjects - Final clinical report; (2) **LSH16/Griffiths:** Pilot Study of Abuse Potential Evaluation of Zolpidem in Outpatient Subjects - Study Summary. *[Vols 1.362 and 1.363]*

Apr 19, 1990 - Chemistry, Manufacturing, and Controls data.

April 25, 1990 - Response to request from Biostatistics for computer data.

Feb 4, 1991 - Supplementary statistical analysis of **Warrington/IGB09**; final report of **LSH25**: Dose Proportionality of Oral Zolpidem in Normal Healthy Volunteers (4 vols); **LSH27**: Relative Bioavailability of Liquid and Solid Forms of Oral Zolpidem in Normal Healthy Volunteers (3 vols).

Feb 18, 1991 - CRFs from US studies for patients treated with zolpidem who experienced a potentially clinically significant laboratory abnormality (PCSA). (26 vols).

Feb 20, 1991 - Computer listings of all laboratory values measured in zolpidem patients in US studies with PCSAs.

Feb 26, 1991 - CRFs not previously submitted from LERS studies for zolpidem patients who had a laboratory PCSA. (8 vols)

Feb 28, 1991 - (1) Randomization schedules for US studies (extracted from Item 11, NDA); (2) line listing of patients who discontinued because of adverse effects or intercurrent illness. *[Vol 1.54/0336]*

Mar 6, 1991 - (1) Proportion tables for lab abnormalities; (2) revised Table II.A.2 *[Vol 1.54/0046]*; (3) table of zolpidem disease state studies.

- cont'd -

Mar 7, 1991 - Listing of all patients (Lorex) who discontinued because of abnormal clinical lab findings.

March 8, 1991 - Table of zolpidem interaction studies.

March 15, 1991 - Reformatted Biopharm data.

May 17, 1991 - Revised labelling.

May 23, 1991 - Update of premedicant data.

June 20, 1991 - Response to query re: statistical analyses.

June 26, 1991 - Response to query re: **LSH14/Jasinski -**

June 28, 1991 - (1) Final study report for **LSH91**; (2) Draft SDA; (3) Response to Chemistry queries; (4) summary of a post-marketing safety study carried out by

3.0 Chemistry

Zolpidem is a novel compound, differing chemically from all currently used hypnotics. Its chemical name is: N,N,6-trimethyl-2-p-tolyl-imidazo[1,2-a]pyridine-3-acetamide L-(+)-tartrate (2:1). It occurs as a white to off-white odorless micro-crystalline powder, sparingly soluble in water (23 g/L at 20°C).

Drug product is prepared in a round, white, film-coated tablet (5 mg) and an oblong white scored film-coated tablet (10 mg). Commercial manufacture is carried out by at its facility at A three-year shelf-life is proposed.

4.0 Pharmacology

The following sections briefly summarize the preclinical and clinical pharmacology of zolpidem.

4.1 Preclinical Pharmacology

In animal studies, zolpidem has been shown to:

a) induce slow wave sleep and maintain a normal sleep pattern;

- cont'd -

b) exhibit anticonvulsant and anxiolytic activity, weak muscle relaxant properties, little effect upon memory acquisition, no effect on respiratory function or platelet aggregation;

c) cause bradycardia and decreased blood pressure in proportion to its hypnotic effect, with no effect on the electrocardiogram;

d) maintain efficacy w/ prolonged treatment without the development of tolerance;

e) exhibit agonist activity at BZD receptors.

In pre-clinical studies, zolpidem has been administered in conjunction with imipramine, theophylline, and aspirin without exacerbating their side-effects, but potentiates the effects of barbiturates.

4.2 Clinical Pharmacology

4.2.1 Summary of Human Pharmacokinetics

In 39 studies and one Lorex study **(LSH03)**, zolpidem was shown to be active in man after oral administration, with a mean T_{max} of 1.8 hrs and a plasma elimination half-life of approx 2.5 hrs (10 hrs in pts with impaired hepatic function). Blood levels increase with dose, but with marked within-subject variability. Absolute bioavailability of the 10 mg scored, coated tablet is 66.4±4.4% (compared with zolpidem 8 mg (1 mg/ml) given as a 30 min IV infusion, with no significant difference among tablet and capsule formulations; see **Warrington/IGB09** *[Vol 1.41/0157]*. Peak concentrations are increased by approx 50% in subjects over 70 yrs of age. Elimination of unchanged drug is less than 0.1% of the administered dose.

Zolpidem is metabolized by oxidation/hydroxylation, with no active metabolites. Protein-binding is approx 60%; in vitro, zolpidem is not displaced by salicylic acid, chlorpromazine, haloperidol, imipramine, or desipramine.

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4.2.2 Other Clinical Pharmacology

Effects of zolpidem on respiratory function, and residual effects on insomniac patients, are discussed under **8.5.5 Special Studies.**

5.0 Proposed Indication(s), Dosage Form and Strength(s), Route of Administration, and Directions for Use

The following text is taken verbatim from the sponsor's 5.17.91 submission.

"AMBIEN (zolpidem) is indicated for the treatment of . short-term insomnia.

while short-term insomnia may last several weeks;

"In polysomnographic studies in both insomnia, AMBIEN has been shown to decrease sleep latency and number of awakenings, to increase total sleep time, sleep efficiency, and to improve quality of sleep.

"In controlled trials of up to three months and open label studies of up to six months in patients with insomnia, there is no evidence of tolerance to zolpidem's hypnotic effect."

a) Dosage forms and strengths:
film-coated tablets 5 mg and 10 mg

b) Route of administration: oral

c) Directions for Use:

"The dose of AMBIEN should be individualized to maximize the beneficial effects on sleep and on wake-time performance.

"The maximum recommended dose for short-term, and insomnias is 10 mg immediately before bedtime.

- cont'd -

"Downward dosage adjustment may be necessary when AMBIEN is administered with agents having known CNS depressant effects because of the potentially additive effects.

"Elderly and/or debilitated patients and patients with hepatic insufficiency may be especially sensitive to the effects of zolpidem. An initial 5 mg dose is recommended in these patients. Total dose should not exceed 10 mg. (see PRECAUTIONS)
"It is recommended that AMBIEN not be prescribed in quantities exceeding a one month supply."

6.0 Description of Clinical Data Sources

As noted under **1.0 Background**, clinical data for this NDA has two sources: the original LERS development program in Europe, the UK, and South America; and the Lorex program under IND A list of all investigators is provided at **Appendix A.**

Data from the LERS studies are included in the Integrated Safety Summary. The LERS data base is not used to support the demonstration of efficacy.

6.1 Primary Development Program

6.1.1 Study Type and Design

LERS' initial development program for zolpidem as an hypnotic consisted of 81 studies, as follows: Phase 1 - 47 trials; Phase 2 - 23 trials; Phase 3 - 11 trials. A total of N=2,412 subjects participated in these trials, including N=1,856 subjects who received zolpidem. As discussed in the next paragraph, routine safety data is available from only 30/81 trials (N=1,825, of whom N=1,336 received zolpidem). It is important to note, however, that deaths and withdrawals for adverse events are counted from <u>all</u> 81 trials. A line listing of the 30 studies in which routine safety data were collected, including one study in children, appears at **Appendix B.** All remaining studies of zolpidem as an hypnotic are listed at **Appendix C.**

- cont'd -

In a separate development program, conducted 13 studies (including one study in children 3-16 yrs of age) to assess the potential of zolpidem as a premedicant. A total of 604/1,100 subjects were exposed to 1-2 doses of zolpidem in the 12 adult studies; a list of these studies is included in **Appendix C.** Safety findings are discussed under **8.5.11 Premedicant Studies.** A synopsis of the study in children was not available at the time of submission, but will be submitted with the first safety update.

Lorex conducted 17 studies of zolpidem as an hypnotic: 9 studies in Phase 1; 6, in Phase 2; and 2, in Phase 3. N=1,184 subjects participated, including N=940 who received zolpidem. The efficacy portion of the NDA is based on the Lorex studies. The sponsor's list of studies in the Lorex program is at **Appendix D.**

The distribution of subjects in the Lorex studies, by study type and drug exposure, is shown below. Because of the use of crossover design in efficacy and Clin Pharm studies, N=201 patients received more than one treatment.

		Lorex Trials Number of Pts Exposed				
Type of Study	Studies	Zolpidem	Active	Placebo	X-O	Total
Clin Pharm	9	122	103	86	125	186
Controlled	6	576	0	256	76	756
Uncontrolled	2	242	-	-	-	242
Totals	17	940	103	342	201	1,184

Thus, the total safety data base for zolpidem was:

Hypnotic	1,856
Premedicant	604
Lorex	940
Total	3,400

- cont'd -

6.1.2 Demographics

A total of 667 females and 346 males were exposed to zolpidem in controlled trials in the 30 trials for which routine safety data was collected. Mean age was 60.2 ±19.7 yrs; mean weight, 61.9 ±13.5 kg. A total of 88 males and 218 females received zolpidem in the uncontrolled trials; age and weight were 63.7 ±16.6 yrs and 66.4 ±14.0 kg, respectively.

The 51 studies for which routine safety data were not collected included 22 controlled studies and 29 open studies (total N=587; 392 male, 195 female); N=520 received zolpidem. Several open studies used subjects of extreme age (80-100 yrs); **Colle/IFR44** studied children (N=12) 6-14 yrs of age. The listing of studies at **Appendix C** gives the sex distribution and age range of all studies.

The 12 adult premedicant studies includes 403 males and 697 females, 16-77 yrs of age.

Three distinct populations were studied in the Lorex program: young adult males (N=186), mean age 28 yrs, in the Clin Pharm studies; a population with a mean age of 35 years in the controlled studies, of whom 507 were male and 251 were female; and in the uncontrolled studies a population, age 42 years, that was equally divided (males, N=119; females, N=123).

Sponsor's Tables summarizing demographic characteristics of the two populations are presented at **Appendix E.** Note that the tabulation is for the 30 hypnotic studies for whom more complete data are available.

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6.1.3 Extent of Exposure

The development program explored doses of zolpidem from 2.5 to more than 35 mg in studies of 1-2 days, 3-7 days, and 8-28 days. In each type of study, 10 and 20 mg were the most commonly tested doses.

The premedicant studies involved single doses of 5-20 mg, with 33 subjects having received 30 mg before that dose was discontinued. In two of eight controlled studies, a dose of zolpidem, lorazepam, midazolam, or placebo was employed as an hypnotic on the night prior to use as a premedicant.

Doses tested in the short-term Lorex trials were 2.5, 5, 7.5, 10, 15, and 20 mg. Both 10 and 15 mg doses were administered in the 31-35 night studies; 15 mg was the primary dose in the uncontrolled long-term study. Of the doses tested, 15 mg was evaluated most often, and for the longest duration.

Sponsor's tabulations of zolpidem dose and duration for the 30 studies and the Lorex studies are presented at **Appendix F**. Premedicant data are at **Appendix C**.

6.2 Secondary Sources

Secondary sources of information regarding the safety and efficacy of zolpidem include non-IND studies, the sponsor's report of post-marketing experience, and the published literature.

6.2.1 Non-IND Studies

Studies carried out as part of the development program are the only non-IND studies of zolpidem.

6.2.2 Post-marketing Experience

Zolpidem has been marketed in France since March, 1988; approximately tablets had been sold at the time of submission of the NDA. The only post-marketing experience reported to date concerns overdoses. See **8.2 Overdose Experience**.

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6.2.3 Literature

There is no scientific literature with respect to zolpidem except for reports of studies included in the present submission. The Lorex trials have produced eight papers:

LSH01 Weintraub M, et al. "Dose ranging by patient preference." Clin Pharm & Ther 41 (2): 207.

LSH02 Merlotti, et al. "The dose effects of zolpidem on the sleep of healthy normals." Sleep Research 17: 51, 1988.

LSH03 Scharf M, Kaffeman M, et al. "Single dose tolerance study of zolpidem." In: Sauvanet, JP, et al, ed. Imidazopyridines in Sleep Disorders. New York: Raven Press. 1988; pp 175-181.

LSH04 Cohn MA, Krall RL. "The effect of hypnotics on the control of breathing: Methods of assessment." In: Sauvanet, JP, et al, ed. Imidazopyridines in Sleep Disorders. New York: Raven Press. 1988; pp 289-297.

LSH08 Koshorek G, Roehrs T, et al. "Dose effects of zolpidem on transient insomnia." Sleep Research 17: 47, 1988.

Vogel G, Thurmond A, et al. "The effects of zolpidem on transient insomnia." Sleep Reserch 17: 67, 1988.

LSH09 Walsh JK, et al. "Experimental phase-advance as a model of transient insomnia and effects of zolpidem." Sleep Research 17: 267, 1988.

LSH12 Carroll PM, Thorpy MJ, et al. "Adverse events in long-term zolpidem treatment in insomniacs." Sleep Res 17: 1988 Abstract. Presented at annual meeting of Association of Professional Sleep Societies, San Diego, Jun 11-15, 1988.

7.0 Efficacy Findings

The discussion of efficacy in this review will focus on the four adequate and well-controlled studies carried out by Lorex, two in . The remainder of the Lorex development program, consisting of two double-blind dose-ranging trials, a long-term safety study, and a dose-preference study, are summarized under **7.2 Other Lorex Studies.**

- cont'd -

7.1 Adequate and Well-controlled Studies

Common features of the Lorex efficacy trials are:

A. Objectives and rationale.

1. One of the efficacy trials in insomnia was carried out in the sleep lab; the other, in outpatient clinics. Both were designed:

a) to evaluate the efficacy of zolpidem compared to placebo in the treatment of patients with insomnia;

b) to determine whether tolerance to the hypnotic effect of zolpidem develops when given to this group of patients in repetitive doses; and,

c) to evaluate the sleep of these patients following abrupt discontinuation of zolpidem.

2. The trials in insomnia were conducted in the sleep lab and were designed to determine the efficacy and safety of zolpidem vs placebo in healthy normals.

B. Population.

1. For purposes of eligibility, insomnia was defined as disturbed or unrefreshing sleep, usually accompanied by daytime fatigue and/or impaired psychomotor performance, for a period of at least one month. Insomnia could occur as part of a medical or psychiatric condition or as a primary sleep disorder.

2. insomnia (several weeks) and insomnia (3 nights or less) were defined as occurring in persons who usually slept normally. Episodes could occur in response to an environmental stressor, eg, cold, noise, or a phase advance produced by flying eastward through three or more time zones. Alternatively, the stimulus could be internal, eg, performance anxiety or grief.

- cont'd -

3. Apart from their sleep histories, males and nonpregnant females 21-60 yrs of age who were in good health were eligible for all studies. Exclusionary criteria were: a medical or psychiatric disorder, including seizures, alcoholism, drug addiction, sleep apnea, nocturnal myoclonus, and mental retardation; use of zolpidem or any other investigational drug within 30 days of start of study; regular use of medication that would interfere with the assessment of an hypnotic; hypersensitivity to benzodiazepines or other CNS depressants; abnormal clinical laboratory tests (incl urine drug screen for benzodiazepines, barbiturates, and drugs of abuse). Shift workers and women who were breast-feeding were also excluded.

4. In most studies, eligibility was confirmed by medical and sleep history, complete physical examination, and clinical lab studies (CBC, urinalysis, SMA-12) at baseline. These were repeated on exit and in event of D/C due to an adverse effect. EKG was required at baseline.

5. In all studies, participants were assigned a patient number in the order in which they entered study. Upon satisfying admission criteria, each subject was then assigned an allocation number, which was the number used in generating randomization schedules. Study reports use both numbers interchangeably; the present review uses allocation numbers exclusively.

C. Efficacy parameters.

1. The therapeutic properties of interest in a sedative-hypnotic are sleep induction and sleep maintenance. The principal measures of efficacy were evaluated both polysomnographically and subjectively, the latter by means of a Morning Questionnaire.

2. Polysomnographic parameters:

a) Latency to persistent sleep (SL) - time in minutes from the beginning of recording to the beginning of the first continuous 10 min of non-wake.

b) Sleep efficiency (SE) - This is a derived measure, calculated as Total Sleep Time (TST) divided by time in bed x 100, and was used by the sponsor as a principal efficacy parameter in all sleep lab studies. TST, the parameter customarily employed in assessing efficacy, is the sum (in minutes) of all Stages 1, 2, 3, 4, REM, and Movement. TST data are available in the statistical packages for the principal sleep lab studies.

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c) Wake time after sleep is initiated - The sum of Wake time during sleep (WTDS - time in minutes from the onset of persistent sleep to the last Stage 2, 3, 4, or REM) and Wake time after sleep (WTAS - time in minutes from the last Stage 2, 3, 4, or REM to end of record).

d) Number of awakenings (NA) - The number of periods awakening of 1 min or longer after the onset of persistent sleep. Each pair of awakenings must be separated by a Stage 2, 3, 4, or REM.

3. Subjective:

a) How long (in min) after bedtime/lights out did you fall asleep?
b) How many times did you wake up during the night?
c) How much time (hrs/min) did you spend awake after falling asleep?
d) How many hours did you sleep last night?

4. Other measures of drug effect:

a) Sleep stages - the time spent in each stage of sleep was reported in minutes and as a percent of TST for the entire night and by thirds of the night. Latencies from the beginning of recording to the first episode of each stage (min and %) were also calculated.

b) Assessments of sleep quality and the refreshing quality of sleep were solicited on the Morning Questionnaire. The scale for both items was: 1=excellent; 2=good; 3=fair; 4=poor.

c) A 5-item Global Impression instrument was administered at the end of all multi-night studies:

"Overall, the medication:
- helped/did not help me sleep
- helped/did not help me sleep faster
- helped/did not help me sleep longer
- helped/did not help me get a better night's sleep
- was strong enough/too strong/too weak."

- cont'd -

D. Patient Enumeration.

As noted above (**6.0 Description of Clinical Data Sources**), the NDA does not utilize any of the study results from the LERS development program in support of efficacy.

The following table enumerates all patients exposed to new drug in the Lorex development program.

	Zolpidem	Active	Placebo	(X-O)	Total
Clin Pharm					
LSH03/Scharf	15	04[a]	-	04	15
LSH04/Cohn	12	12[b]	12	24	12
LSH05/Leese	05	10[b]	-	05	10
LSH06/Leese	31	29[b]	30	-	90
LSH07/Cohn	14	08[b]	-	08	14
LSH13/Jasinski	04	04[c]	04	08	04
LSH14/Jasinski	14	14[c]	14	28	14
LSH15/Griffiths	09	05[a]	09	14	09
LSH16/Griffiths	18	17[a]	17	34	18
Totals	122	103	86	125	186
Controlled					
Chronic/acute					
LSH17/m'center	51	-	24	-	75
LSH19/m'center	87	-	53	-	141
Transient					
LSH08/m'center	360	-	102	-	462
LSH09/Walsh	31	-	31	31	31
Dose range					
LSH02/Roth	12	-	12	12	12
LSH11/Scharf	35	-	34	33	35
Totals	576	-	256	76	756
Uncontrolled					
LSH01/Weintraub	13	-	-	-	13
LSH12/Mendels	229	-	-	-	229
Totals	242	-	-	-	242
TOTALS	940	103	342	201	1,184

[a] Triazolam; [b] codeine phosphate; [c] diazepam.

Reviews of the Lorex trials follow.

- cont'd -

LSH17: "The effect of zolpidem in patients with chronic insomnia."
[Synopsis - Vol 1.53/0034; full report - Vol 1.95]

Investigators: T Roth, Sleep Disorders Center, Henry Ford Hospital, Detroit, MI; MB Scharf, Center for Research in Sleep Disorders, Cincinnati, OH; GW Vogel, Sleep Laboratory, Georgia Mental Health Institute, Atlanta, GA; JK Walsh, Sleep Disorders Center, Deaconess Hospital, St Louis, MO.

Study Plan

1) Objectives/rationale: As stated above.

2) Inclusion criterion: chronic (≥3 mo) insomnia as defined by sSL greater than 30 min, sTST at least 4 but less than 6 hrs per night, and daytime complaints associated with disturbed sleep. Eligibility confirmed in sleep lab: SL≥20 min and TST=240-420 min on 2/3 screening nights.

3) Design: Multicenter double-blind, randomized study. One week single-blind placebo run-in; 35-night double-blind treatment; three-day single-blind placebo withdrawal period.

a) Treatment groups: Balanced parallel groups were to receive zolpidem 15 mg (Z15), zolpidem 10 mg (Z10), and placebo (Pla), two capsules per night. All subjects received placebo during screening, run-in and withdrawal periods.

b) Randomization: Five subjects were to be assigned at random to each treatment group at each of 4 study centers (N=15/center, 20/Rx) after final eligibility had been determined. Computer-generated randomization schedules were prepared by the sponsor and maintained at its offices.

c) Blinding/dosage forms: All study drugs were provided by Lorex in blisterpacks carrying the subject's allocation number and containing 9 doses. Each dose consisted of 2 capsules containing zolpidem 10 mg, zolpidem 5 mg, or matching placebo. Unused medication was to be returned and counted.

d) Time sequence: Subjects were evaluated in the sleep lab for 1 drug-free Adaptation night and three Screening nights prior to randomization; thereafter, on the first two nights of each week. Morning Questionnaires, vital signs, and brief neurological exam were recorded and performance tests were carried out in the morning following each night in the sleep lab. On all remaining nights, subjects took assigned medication at home.

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Week	Study night	Medication	Location	Purpose
Screen	-4	Pla	Lab	Adaptation
	-3 to -1	"	"	Screening
1	1,2	"	"	Baseline
	3-7	"	Home	"
2	8,9	Treatment	Lab	Acute
	10-14	"	Home	"
3	15,16	"	Lab	Intermediate
	17-21	"	Home	"
4	22,23	"	Lab	"
	24-28	"	Home	"
5	29,30	"	Lab	"
	31-35	"	Home	"
6	36,37	"	Lab	Long-term
	38-42	"	Home	"
7	43-45	Pla	Lab	Abrupt D/C

e) Rules for dropouts: Subjects who withdrew from the study were to be replaced with new subjects assigned to the same treatment.

f) Duration: Study design required each subject's participation for 8 weeks. Overall duration was not specified.

g) Dosing plan: All subjects were to take two capsules 30 min before bedtime on each night of study.

h) Concomitant medications: No short-acting CNS medications or alcohol were to be taken within 12 hrs of any screening night and were to be discouraged throughout the study. Occasional use of cold preparations was not contraindicated; patients were encouraged not to take antihistamines.

i) Primary efficacy assessments: PSG parameters.

j) Secondary efficacy parameters: Morning Questionnaire (sleep lab only); Global Impression scale.

k) Other outcome measures:

i) on sleep lab nights: 6-item Evening Questionnaire (naps; concomitant medications; adverse events; use of food, alcohol, and caffeine); Adverse Events questionnaire; Performance tests (Digit Symbol Substitution Test and Digit Symbol Copying Test);

ii) at home: Sleep Log (nights 3-7 each week).

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4) Types of statistical analysis: Evaluation of efficacy was based on means of two nights. When the value for one night was missing, the value for the other night was used. Data were pooled. Tests of treatment effect were based on unadjusted outcomes; for SL and SE, analysis of change from baseline was carried out as a secondary analysis. Each efficacy measure was compared among treatment groups using analysis of variance (treatment, center, and treatment-by-center interaction). When the overall effect was significant, pairwise comparisons of the mean square error from the ANOVA were made using Fisher's Least Significant Difference method.

5) Tolerance was assessed by comparing the results for the last week of active treatment with results for the first week. To assess post-treatment effects, both the daily means and the change from baseline of the efficacy variables during the first week after active treatment were compared among the three treatment groups. All tests of significance were two-tailed, p=.05. Sample size of N=20/Rx provided 80% power for determining that mean decreases in sleep latency of 45 min, 40 min, and 10 min for Z15, Z10, and Pla, respectively, differed significantly. All analyses based on the Intent-to-treat data set.

Study Conduct

1) Patient Disposition: A total of 178 subjects was screened for study; 75 were found eligible and were randomized to treatment (Scharf 26, Roth 18, Vogel 15, Walsh 16). Of this number, 67 completed study, including the three days of post-treatment placebo. There were no discontinuations due to lack of efficacy. Dr Scharf enrolled more subjects than the other investigators at the sponsor's request.

Screened		178	
Randomized		75	
	Z15=25	Z10=26	Pla=24
Completed	22	22	23
Discontinued	3	4	1

Z15: **Roth #105** - Day 21 [after night 21], adverse event (dizziness, drowsiness, nausea)
Walsh #405 - Day 13, adverse event (visual disturbance, oversedation)
Scharf #204 - Day 33, intercurrent illness
Z10: **Scharf #211** - Day 19, non-compliance
Walsh #414 - Day 24, moved
Roth #112 - Day 33, change in work schedule
Vogel #311 - Day 19, change in work schedule
Pla: **Roth #106** - Day 12, intercurrent illness

- cont'd -

Vogel #303/Pla completed one screening night, dropped out because of intercurrent illness (flu syndrome), and subsequently re-entered and completed study as **#305/Z15.**

2) Demographics/group comparability: There were no statistically significant differences among treatment groups with respect to age, sex, race, weight, height, and sleep history at empanelment. Principal means are shown below.

Variable	Z15 N=25	Z10 N=26	Pla N=24	Total N=75	p-value
Male	10	11	6	27	
Female	15	15	18	48	.280
Age (yrs)	38	37	38	-	.702
S.D.	11	12	12		
Usual sleep latency (min)[a]	4.5	4.5	4.8	-	.145
Usual sleep time (hrs)[b]	2.7	2.7	2.5	-	.463
Duration of insomnia (yrs)	7.5	7.8	11.2	-	.206
Prior use of hypnotic	11	11	10	-	.855

[a] 1, <15 min; 2, 15-29 min; 3, 30-44 min; 4, 45-59 min; 5, >60 min.
[b] 1, <4 hrs; 2, 4-5 hrs; 3, 5-6 hrs; 4, 6-7 hrs; 5, >7 hrs.

3) Dosing information: All subjects who received medication had some followup data and are included in the Intent-to-treat data set. Data for individual nights from five patients were excluded:

Roth #118 (Z15) - Night 16 (not on study medication)
Vogel #304 (Z10) - Nights 15,16 (missed Rx on night 14)
Walsh #404 (Z10) - Night 16 (missed scheduled bedtime)
#411 (Z10) - Nights 43-45 (missed Rx on night 42)
Roth #107 (Pla) - Nights 29,30 (missed Rx on night 28)

4) Concomitant medications: Six subjects took an antihistamine or decongestant one or more times during the trial: **Roth #118; Scharf #202** and **#214; Vogel #307; Walsh #411** and **#415. Scharf #206** and #223 took antihistamines regularly.

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5) Efficacy: Treatment groups differed at baseline on SE (85% for Z10 vs 81% for Z15 and Pla) but not on SL. Statistically significant improvement vs placebo was evident for the Z15 group in the first week in both SL (47 min to 22 min) and SE (81% to 88%) and persisted to the end of the trial. Similar results were seen for Z10 (SL, 36 to 23 min; SE, 85% to 88%) for all but the last week of active treatment. Z15 and Z10 did not differ; no PSG measure of wake time after sleep onset showed a drug effect. There were no post-treatment differences from placebo.

6) Principal efficacy data are shown below. Note that Nights 8 and 9 were the first two nights of active treatment; Nights 43-45 reflect acute discontinuation. Analysis of sleep efficiency was performed on the logit of the efficiency.

Primary PSG efficacy variables:
mean scores and significance levels

	Nights						
	1-2	8-9	15-16	22-23	29-30	36-37	43-45
Z15 (N=25)							
SL (min)	47	22*	26*	22*	29*	28*	48
SE (%)	81	88*	88*	89*	88*	87*	80
NA	9	8	8	8	9	8	8
Z10 (N=26)							
SL (min)	36	23*	24*	20*	24*	26	47
SE (%)	85*	88*	88*	88*	89*	88	83
NA	8	6	7	6	7	7	7
Pla (N=24)							
SL (min)	50	45	51	56	44	48	43
SE (%)	81	82	80	82	83	81	82
NA	7	7	6	7	6	7	6

* All comparisons vs placebo, $p < .05$, two-tailed.

7) Subjective assessments: Subjective estimates of efficacy, as measured on the Morning Questionnaire, supported the results of polysomnography. sSL was significantly shorter in the Z15 group than in Pla at every timepoint during double-blind treatment; Z10 was better than Pla at Weeks 4 and 5. sTST was significantly longer in the Z15 group than in Pla at Weeks 4 and 5; in the Z10 group, at Week 5. Other measures of sleep maintenance from the Morning Questionnaire (number of awakenings and time awake after falling asleep) were non-significant vs placebo, with the exception of number of awakenings for the Z15 group at Week 2.

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Principal subjective efficacy parameters: mean values and significance levels

	Nights						
	1-2	8-9	15-16	22-23	29-30	36-37	43-45
Z15 (N=25)							
sSL (min)	61	34*	31*	32*	35*	32*	78
sTST (min)	332	394	384	397*	389*	394	341
sNA	4	2*	2	2	2	2	3
Z10 (N=26)							
sSL (min)	57	44	35	38*	38*	38	62
sTST (min)	331	361	362	356	358*	369	333
sNA	4	3	3	3	3	3	4
Pla (N=24)							
sSL (min)	70	61	63	73	69	57	48
sTST (min)	331	355	351	340	325	356	369
sNA	3	2	2	2	3	2	2

* All comparisons vs placebo, p <.05, two-tailed.

8) Sleep architecture: Stage 3-4 sleep was unaffected; REM sleep was decreased by Z15 during acute administration (from 19.8% to 18.8% on Days 8 and 9, and to 18.2% on Days 15 and 16, both results p=.05, two-tailed), but was otherwise unaffected.

9) Other variables: Quality of sleep was perceived as improved vs Pla only by the Z15 group and only at the last week of active treatment. At Week 7 (post-treatment), both zolpidem dose groups had poorer sleep quality than Pla.

10) Post-treatment effects: The effect of discontinuing medication was evaluated among the three treatment groups by comparing mean results for each night of the post-treatment period and mean changes for each group from pre-treatment baseline. There was no evidence of deterioration in sleep.

11) Conclusions: The results of the study demonstrate the efficacy of zolpidem in a daily dose of 15 or 10 mg in the treatment of insomnia for up to 30 days. There was no evidence of withdrawal, and no suggestion of the development of tolerance. Independent review by Biostatistiacs (HFD-713) gave results that are in agreement with those of the sponsor.

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"The effect of zolpidem in outpatients with insomnia."
[Synopsis - Vol 1.53/0040; full report - Vol 1.101]

Investigators: J Cohn, Psychopharmacology Research Institute, Long Beach, Ca; JM Fillingim, Savannah. Ga; HW Lahmeyer, Univ of Illinois Hospital, Chicago, Ill; I Leppik, University of Minnesota, Minneapolis, Minn; J Kann, Biodecision Laboratories, Pittsburgh, Pa; J Docherty, Brookside Hospital, Nashua, NH.

Study Plan

1) Objectives/rationale: As stated. Originally planned for 4 centers.

2) Inclusion criterion: Same as

3) Design: Multicenter double-blind randomized; 3-day single-blind baseline placebo; 31-day double-blind treatment; 4-day single-blind post-treatment placebo period.

a) Treatment groups: Same as except that treatment groups were unbalanced (4:4:5) in anticipation of a 15% higher withdrawal rate for Pla subjects.

b) Randomization: Ten subjects were to be randomly assigned to each treatment group at each site; total N/Rx=40. Otherwise, same as

c) Blinding/dosage forms: Same as

d) Time sequence: Subjects evaluated at home. Morning Questionnaires were completed on Days 1, 2, 3, and 7 of each study week. Weekly followup on Days 7, 14, 21, 28, and 35: medication packets, Questionnaires, and Sleep Logs were collected and new ones issued; vital signs were recorded; adverse effects were sought by questioning.

Week	Night	Medication	Purpose
1	1-3	Placebo	Baseline
	4-7	Treatment	Acute Rx
2	8-14	"	Intermediate Rx
3	15-21	"	"
4	22-28	"	"
5	29-34	"	Long-term Rx
	35	Placebo	Abrupt D/C
6	36-38	Placebo	Abrupt D/C

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Thus, the first recorded evaluation of study drug was after Night 7, which was the 4th night of active treatment. The analysis of efficacy variables was based on the mean values for the four consecutive days on which the Questionnaires were completed (eg, the value for Acute Rx was the mean of Week 1/Day 7 and Week 2/Days 8, 9, and 10).

e) Rules for dropouts: Subjects who withdrew were not to be replaced, but enrollment was to continue until 30 subjects had completed study at each site. Reason for discontinuation was to be recorded on the CRF.

f) Duration: Study design required each subject's participation for 38 days. Overall duration was not specified.

g) Dosing plan: Same as ie, all subjects were to take two capsules 30 min before bedtime on each night of study.

h) Concomitant medications: Triazolam was not to be taken within 3 nights of empanelment; other short- or intermediate-acting benzodiazepines, within 7 nights; long-acting benzodiazepines were prohibited throughout the study. Use of other short-acting CNS medications or alcohol was to be discouraged.

i) Primary efficacy assessments: Morning Questionnaires.

j) Secondary parameters: Global Impression (Day 43).

4) Types of statistical analysis: Data pooled. There is no discussion of statistical treatment of baseline demographic data in the protocol. All efficacy analyses were based on the Intent-to-treat population. Primary efficacy variables were to be assessed by analysis of variance, including effects for treatment, center, and their interactions. Pairwise comparisons were to use the mean square error from the ANOVA. Level of significance for all tests was set at p=0.05, two-tailed. The sample size of N=40/Rx was estimated to provide 80% power for determining that mean decreases in sleep latency of 30 min, 25 min, and 10 min for Z15, Z10, and Pla, respectively, were significanctly different.

Study Conduct

1) Patient Disposition: A total of 178 subjects was screened; 145 were found eligible and were randomized to treatment. Of this number, 118 completed study. Data from Docherty and Kann were combined for all statistical analyses. The data are shown on the next page.

- cont'd -

Screened				178
Randomized				145
	Z15=46	Z10=45	Pla=54	
D/C on BL/plac	3	1	0	4
D/C on active	6	7	10	23
Completed	37	37	44	118

		Randomized			
	Screened	Z15	Z10	Pla	Completed
Docherty	16	5	4	5	12
Fillingim	32	10	10	12	32
Lahmeyer	30	8	8	10	18
Cohn	35	8	7	9	17
Kann	29	5	6	6	15
Leppik	36	10	10	12	24
TOTALS	178	46	45	54	118

2) Discontinuations on active:

	Z15	Z10	Pla	Total
	N=43	N=44	N=54	N=141
Adverse event	3	4	0	7
Lack of efficacy	0	3	5	8
Int'current illness	1	0	1	2
Missed appointment	1	0	1	2
Lost to followup	0	0	1	1
Administrative	0	0	1	1
Non-compliance	1	0	0	1
Concurrent Rx	0	0	1	1
TOTALS	6	7	10	23

3) Demographics: Treatment groups were similar in demographic characteristics. Mean TST for Cohn Z15 was approx 60 min longer than for the Pla group.

Variable	Z15	Z10	Pla	Total	p-value
Age (yrs)	44	47	44	-	.217
Range				-	
N under 50	31	25	35	91	
N over 50	15	20	19	54	.477
Sex					
Male	20	22	22	64	
Female	26	23	32	81	.730

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Weight (kg) Range	73	76	74	74	.697
Usual SL (min)	75	65	58	67	.340
Subj TST (min)	308	316	315	313	.975
Number of awakes	3	2	3	3	.916

4) Dosing information: All subjects who received medication had some followup data and are included in the Intent-to-treat data set. Data from 140 nights were excluded, as follows:

Site	N'/N[a]	B/L	Z15	Z10	Pla	Post-Rx	Total
Cohn	11/24	5	2	7	8	0	22
Fillingim	5/32	0	5	1	3	0	9
Lahmeyer	13/26	0	10	7	15	3	35
Leppik[b]	10/32	8	10	3	27	6	54
Kann	4/17	2	4	3	2	0	11
Docherty	6/14	0	6	0	3	0	9
TOTALS	49/145	15	37	21	58	9	140

[a] N' with excluded data / N randomized.
[b] All data for two subjects (**#416/Z15**, 12 nights; **#406/Pla**, 23 nights) were disqualified because of prohibited concurrent medications (codeine and marijuana, respectively).

5) Efficacy: Results, by week, based on the Intent-to-treat population, are shown below. Values for each period are mean responses during 4 nights of drug administration; responses for the first three nights of active are not recorded.

Primary subjective efficacy parameters: mean scores and significance levels

	Baseline	7-10	14-17	21-24	28-31	35-38
Z15						
sSL (min)	76	38*	33*	33*	33	70
sTST (min)	308	378*	384	375	385	332
sNA	3	2*	1*	1	1	2
Z10						
sSL (min)	65	34*	34*	32*	27*	54
sTST (min)	316	377*	373	375	390	354
sNA	2	1*	1	1	1	2

- cont'd -

Pla						
sSL (min)	58	61	50	61	43	46
sTST (min)	315	331	348	344	360	359
sNA	3	2	2	2	2	2

* All comparisons vs placebo, p <.05, two-tailed.

6) Z15 was associated with a 50% decrease in sSL, and Z10 with a 48% decrease. Both doses maintained efficacy in sleep induction throughout treatment; post-treatment values returned to baseline.

7) There was a 23% increase in sTST during the first week of treatment with Z15, and a 19% increase with Z10; both strengths were associated with nonsignificant post-treatment increases above baseline.

8) Both actives yielded statistically significant decreases in sNA in the first week of treatment.

9) Sleep Quality was improved for both strengths in the first week of treatment, and for Z15 in the second week.

10) Conclusions: The results of the study demonstrate the efficacy of zolpidem in a daily dose of 15 or 10 mg in the treatment of insomnia for up to 30 days. There was no evidence of withdrawal, and no suggestion of the development of tolerance. Independent review by Biostatistics (HFD-713) gave results that are in agreement with those of the sponsor.

"Dose-response efficacy study of zolpidem in subjects with insomnia."
[Synopsis - Vol 1.53/0021; full report - Vol 1.75]

Investigators: T Roth, Detroit, MI; GW Vogel, Atlanta, GA.

Study Plan

1) Objectives/rationale: To determine a) the efficacy of zolpidem 10 and 7.5 mg vs placebo in healthy normal subjects with transient insomnia; b) the tolerance of these subjects to zolpidem; and c) their psychomotor impairment vs placebo approx 10 hrs post-drug. Additionally, to evaluate dose-related effects of zolpidem at doses of 20, 15, and 5 mg in the same population.

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The study was carried out in the sleep laboratory, using as a model of insomnia the so-called "first-night" effect (Rechtschaffen and Verdone, 1964; Dement, Kahn, and Roffwarg, 1965; Agnew, Webb, and Williams, 1966) which typically results in a longer latency to persistent sleep, more awakenings, more total wake time, and a decrease in the percent stage REM compared with findings on subsequent nights for lab-naive subjects.

2) Inclusion criteria: Subjects were required to be non-insomniac, as evidenced by a usual sTST of 6 hrs or more and a usual sSL of 30 min or less. Persons with a history of having spent one or more nights in a sleep laboratory were excluded.

3) Design: Two-center double-blind, randomized, single-night parallel groups sleep laboratory study of 5 doses of zolpidem vs placebo.

a) Treatment groups: Unbalanced parallel groups were to receive 20, 15, 10, 7.5, or 5 mg zolpidem or matching placebo.

b) Randomization: N=100 subjects were to be randomly allocated to each of the three primary efficacy groups (Z10, Z7.5, and Pla); N=50 were to be assigned to each of the other groups, namely, Z20, Z15, and Z5. Allocation to a treatment group followed screening; randomization was stratified by center, each investigator being responsible for 225 subjects. Randomization schedules were prepared by the sponsor and maintained at its offices.

c) Blinding/dosage forms: All study drugs were prepared by Lorex in blisterpacks carrying the subject's allocation number and containing a single dose consisting of 3 capsules of zolpidem 2.5 or 10 mg or matching placebo.

d) Time sequence: Subjects were evaluated in the sleep laboratory for one night (Total bed time = 480 min). Vital signs were recorded and a breathalyzer test was administered prior to dosing. In the morning, vital signs were recorded; a sleep questionnaire (sleep efficiency and quality) was administered, performance tests (Digit Symbol Substitution Test and Symbol Copying Test) were carried out, and heel-to-toe gait was assessed. A mail-in questionnaire was used to elicit late-occurring adverse effects. Post-treatment physical examination was at the discretion of the invetigator.

e) Rules for dropouts: All subjects were required to complete study within three weeks of screening; those not completing study because pre-dose alcohol screen was positive or because of noncompliance with study procedures were not to be replaced.

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f) Duration: One night.

g) Dosing plan: All subjects took 3 capsules with water 30 min before lights out.

h) Concomitant medications: As stated. No medication was to be taken on study day without the investigator's permission, and no naps longer than 60 min were permitted. No food, coffee, tea, or other caffeinated beverage was permitted after 7 pm on study day. Blood alcohol level of ≤.02% was acceptable.

i) Primary efficacy parameters: PSG parameters.

j) Secondary efficacy parameters: Subjective estimates of sleep efficiency and sleep quality.

k) Other outcome measures: Performance tests to evaluate residual drug effects; mail-in questionnaires.

4) Types of statistical analyses: Data were pooled. Categorical variables were summarized by frequency distribution; continuous variables, by means and standard deviations.

a) Treatment groups were compared with respect to demographics, sleep histories, and vital signs. tests were used for categorical data; two-way analysis of variance was applied to continuous data. tests were used to adjust for investigator effect in the comparison of dichotomous variables across treatment groups.

b) Efficacy was assessed by two-way analysis of variance, incorporating effects for treatment (6 levels), investigator (2 levels), and their respective interactions. In the event a significant ($p \leq .05$) overall treatment difference was observed, pairwise comparisons, restricted to the placebo vs Z10 and Z7.5, were performed by t-tests using the mean square error from the ANOVA. The same model was also used for the other PSG parameters, the morning questionnaire, and the performance tests.

c) Linear regression analysis of data from all dose groups was used to determine dose-relationships of primary variables. A model with linear and quadratic terms was initially fitted and terms were then dropped in a stepwise fashion; the resulting model was tested for goodness of fit.

d) Pairwise treatment comparisons were two-sided, $p \leq .05$.

e) No statistical comparisons were carried out by the sponsor for the 20 and 5 mg doses.

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Study Conduct

1) Patient Disposition: A total of 595 subjects was enrolled; disposition was as follows:

	Roth	Vogel	Total
Screened	307	288	595
Not randomized	72	61	133
Failed screening	31	31	62
Interc'nt illness	1	0	1
Prohibited concom Rx	2	1	3
Non-compliant	5	0	5
Withdrew	14	3	17
Lost to followup	19	17	36
Not needed	0	9	9
Randomized	235	227	462

2) Demographics/group comparability: 79% of randomized subjects were male, 83% were white (mean age 30.9 yrs, range: yrs). There were no statistically significant differences among the treatment groups with respect to demographic variables.

	Z20	Z15	Z10	Z7.5	Z5	Pla	Tot
N	51	51	104	102	52	102	462
Gender							
Male	42	38	85	82	36	83	366
Female	9	13	19	20	16	19	96
Race							
White	40	44	87	86	43	84	384
Other	10	4	13	12	6	15	78
Age (yrs)							
Mean	29	31	30	30	33	32	31
S.D.	9	10	11	9	12	11	10
Weight (kg)							
Mean	79	76	74	75	74	77	76
S.D.	16	14	12	14	14	13	14
Height (cm)							
Mean	176	176	176	175	172	175	175
S.D.	8	10	9	9	10	10	10

3) Dosing: One Roth subject (Z7.5) did not take study medication, and two Roth subjects (Z10, Pla) did not complete Total bed time (480 min). All remaining 459 subjects were included in the Intent-to-treat data set.

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Records of 24 subjects who completed the study were disqualified for the following reasons:

	Roth	Vogel	Total
Positive drug screen	9	2	11
Caffeinated beverage w/i 2 hrs of bedtime	4	6	10
Daytime nap greater than 60 min	3	0	3

Distribution of the evaluable data set was as follows:

	Z20	Z15	Z10	Z7.5	Z5	Pla	Tot
Roth	25	26	50	48	24	46	219
Vogel	25	24	47	49	25	49	219
TOTALS	50	50	97	97	49	95	438

4) Efficacy: Both Z10 and Z7.5 were associated with statistically significant differences vs placebo in the three principal PSG measures of efficacy.

Efficacy parameters:
mean scores and significance levels

	Z10	Z7.5	Pla	p-value[a]
N size	104	102	102	-
SL (min)	17.4*	17.0*	27.1	.003
SE (%)	91.8*	91.7*	87.8	.001
NA	5.3*	5.0*	6.7	.024
Stage 3/4 (%)	13.6	15.7*	12.4	.041
Stage REM	18.5*	18.4*	20.9	.001
sSL (min)	18.2*	18.9*	28.8	.001
sTST (hrs)	7.2	7.3	7.1	.263
Sleep quality[b]	2.2*	2.2*	2.7	.001
Refreshing sleep[b]	2.1	2.1	2.3	.083

[a] Overall treatment comparisons for six groups.
[b] 1=excellent; 2=very good; 3=fair; 4=poor.
* p <.05, two-tailed, vs placebo.

5) Sleep architecture: An increase in Stage 3/4 (15.7 vs 12.4) and a decrease in Stage REM (18.4 vs 20.9) were reported for Z7.5 vs Pla; decreased Stage REM (18.5) was also reported for Z10.

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6) Subjective assessments: sSL was shortened for both Z10 and Z7.5 in comparison with Pla, but not sTST. Subjective estimates of sleep quality vs Pla reached statistical significance for Z10 and Z7.5; estimates of refreshing quality of sleep did not.

7) Conclusions: The results of the study demonstrate the efficacy of zolpidem in a dose of 10 or 7.5 mg in the treatment of insomnia. There was no evidence of withdrawal. Independent review by Biostatistics (HFD-713) gave results that are in agreement with those of the sponsor.

"Dose-response study of the effect of zolpidem on insomnia produced by 3-hr phase advance."
[Synopsis - Vol 1.53/0023; full report - Vol 1.78]

Investigator: JK Walsh, St Louis, MO.

Study Plan

1) Objectives/rationale: To evaluate the relationship between dose and the effect of zolpidem on sleep when given to subjects undergoing a 3-hr phase advance; to evaluate the relationship between dose and the effect of zolpidem on psychomotor performance following awakening in subjects undergoing a 3-hr phase advance; to evaluate the efficacy and safety of zolpidem as compared to placebo in subjects undergoing a 3-hr phase advance. Such a phase advance typically produces increased SL and increased NA during the first part of the night, and is the type of sleep disturbance commonly seen with eastbound air travel.

2) Inclusion criterion: As for ie, subjects were required to be non-insomniac, as evidenced by a usual sTST of 6 hrs or more and a usual sSL of less than 30 min. Subjects considered eligible on the basis of medical and sleep history, physical examination and clinical laboratory studies underwent a two-night medication-free evaluation in the sleep laboratory (Total bed time, 480 min) to rule out significant sleep disorders and confirm eligibility by PSG criteria: SL less than 20 min; TST at least 420 min. The first night also served as an Adaptation night.

3) Design: Double-blind, randomized balanced crossover sleep lab study of single doses of zolpidem 5, 10, 15, or 20 mg vs placebo. Study was composed of two independent 3-period crossovers. Each subject participated in one, but not both, crossovers.

- cont'd -

		Crossover I Period			Crossover II Period		
		1	2	3	1	2	3
Seq:	I	Pla	Z10	Z20	Pla	Z5	Z15
	II	Z20	Pla	Z10	Z15	Pla	Z5
	III	Z10	Z20	Pla	Z5	Z15	Pla

a) Randomization: A total of N=30 subjects was tc be enrolled, 15 in each Crossover. Each subject was randomly assigned to one of the six sequences. Randomization schedules were computer-generated by the sponsor and maintained at its offices.

b) Blinding/dosage forms: As for ie, all study drugs were prepared by Lorex in blisterpacks carrying the subject's allocation number and containing a single dose consisting of 3 capsules of zolpidem 10 mg, 2.5 mg, or matching placebo.

c) Time sequence: The 3 treatments within each crossover were tested in three separate periods, with 5-10 days separating periods. Each period consisted of two consecutive study nights: placebo 30 min before usual bedtime (determined uniquely for each individual) on the first night and, on the second night, study drug advanced 3 hrs compared to Night 1. Vital signs were recorded prior to bedtime and upon awakening. Following a.m. toilet and dressing, subjects also completed a Morning Questionnaire, the DSST, and the DSCT. The Stanford Sleep Latency Test was administered one and three hrs after the PSG recording was terminated. Heel-to-toe gait test was carried out and vital signs were recorded prior to departure from the laboratory.

d) Rules for dropouts: Subjects who withdrew from the study were to be replaced; replacement subjects were to be assigned the same treatment sequence as the subject they replaced. Records of subjects withdrawing for any reason were reviewed for safety.

e) Duration: Complete study required 8 nights in the sleep laboratory: 2 for screening/adaptation, and 2 for each period of the crossover.

f) Dosing plan: All subjects took 3 capsules with water 30 min prior to bedtime on each study night.

g) Concomitant medication: No medication other than study drug was to be taken on study days without investigator approval. No alcohol or napping was permitted on study days; no food or caffeinated beverages were permitted once subjects had arrived at the sleep laboratory.

- cont'd -

h) Primary efficacy assessments: PSG parameters.

i) Secondary efficacy parameters: Subjective estimates of sleep efficiency and sleep quality.

j) Other outcome measures (related to safety): frequency and severity of adverse effects; changes in vital signs; Performance tests; Sleep Latency Test; mail-in questionnaire.

5) Types of statistical analysis: Within each crossover, an analysis of variance was carried out for each sleep parameter, incorporating effects for subject, period, and dose. Where a difference was observed, pairwise comparisons were made with placebo. Sample size was such that the study had a power of 80% for detecting a 10% difference in sleep efficiency for an active drug vs placebo (alpha = 0.05). Sleep responses were also to be regressed against dose to determine a dose response.

Study Conduct

1) Patient disposition: A total of 53 subjects was enrolled; disposition was as follows:

Randomized = 34
Not randomized = 19

SL greater than 20 min	6
Refused to participate	4
Lost to followup	2
Noncompliance	2
Abnormal labs	2
Sleep apnea	1
Recent psychiatric Rx	1
Hypersensitivity to BDZs	1

Three subjects (**#106, #111, #118**) were randomized to Z20/Pla/Z10, but were discontinued by the investigator after Night I of the first period due to noncompliance and were not exposed to study medication. Their replacements were **#132** (Z20/Pla/Z10), **#139** (Z10/Z20/Pla), and **#141** (Z20/Pla/Z10).

	Crossover I	Crossover II	Total
Randomized	18	16	34
Data excluded	5	0	5
Completed/evaluable	13	16	29

2) Demographics: Of the 31 subjects who completed the study, 29 were male and 27 were white; mean age was 24.0 yrs.

- cont'd -

	Crossover I	Crossover II
N	18	16
Sex		
Male	14	15
Female	1	1
Race		
White	13	14
Other	0	2
Age (yrs)		
Mean	25	23
Range		
Weight (kg)		
Mean	76	74
Range		
Height (cm)		
Mean	176	175
Range		

3) Dosing information: All subjects who received study medication had some followup data and are included in the Intent-to-treat data set (N=31). Efficacy data for two subjects who completed study were excluded from analysis:

a) Subject #107 (Z10/Z20/Pla) - Admitted to study although screening SL was 25.5 min; SL greater than 60 min during Night 1 of each of the three study periods. All data excluded.

b) Subject #132 (Z20/Pla/Z10) - Change in work schedule after first study period resulted in 2 hr advance in routine bedtime. All data excluded.

c) Subject #121 (Pla/Z10/Z20) had his bedtime delayed 85 min on Night 2 of the third period and vomited shortly after bedtime, causing further delay. Data for third period excluded.

4) Since normal baseline sleep and the 3-hr phase advance were prerequisites for this model of insomnia, the Evaluable data set rather than the Intent-to-treat data set, was used in the primary analysis. Where necessary to improve distributional characteristics, the data were transformed using the natural logarithm of SL and the logit of SE.

5) Concomitant medications: None.

6) Effects of placebo: The following table displays mean values (SD in parentheses) for Sleep Efficiency and Sleep Latency for all placebo treatments in the Evaluable data set.

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	Crossover I	Crossover II	Overall
Night 1	N=38	N=48	N=86
SE %	94 (3)	95 (3)	95 (3)
SL min	12 (11)	6 (5)	9 (9)
Night 2	N=13	N=16	N=29
SE %	84 (13)	86 (14)	85 (13)
SL min	25 (38)	13 (12)	18 (27)

For the three Night 1 placebo treatments of Crossover I, a total of 38 PSG records were available (one for each night for each of 13 subjects, except for the third Night 1 for Subject #121); for Crossover II, 48 records. Although the mean SE during phase advance under placebo treatment was 85%, compared with 95% at baseline, 16/29 subjects (6 in Crossover I and 10 in Crossover II) were affected only minimally, with SEs greater than 90%.

7) Efficacy: SL did not improve at any dose; SE showed statistically significant ($p = .034$) improvement on the ANOVA; pairwise comparison of Z5 and Z15 showed that both were superior to placebo. Of the two measures of sleep maintenance, Wake Time During Sleep showed the effects of treatment, with statistically significant improvement on Z10 and Z20; there was no effect on Number of Awakenings.

	Crossover I N=13			Crossover II N=16		
	20 mg	10 mg	Pla	15 mg	5 mg	Pla
SL (min)	26	17	25	6	10	13
SE (%)	89	93	84	94*	93*	86
WTDS	19*	20*	54	19	24	46
NA	5	5	4	5	5	6

* $p < .05$, two-tailed, vs placebo.

8) Further analysis of the SE data, comparing the results for study drug with those for pooled placebo, showed that the effect of zolpidem was confined to the first 4 hrs of each night's recordings:

	20 mg	15 mg	10 mg	5 mg	Pla
SE (%)					
First 4 hrs	88	96*	92*	94*	82
Second 4 hrs	90	92	93	92	88

* $p < .05$, two-tailed, vs placebo.

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9) Sleep architecture: Principal effects of zolpidem on sleep staging were an increase (vs placebo pooled across both Crossovers) in % Stage 2 with Z5 and Z15 and a decrease in % Stage REM with Z15 and Z20. The only other statistically significant finding was a decrease in % Stage 1 with Z15. Data are shown below:

	% Sleep Stages				
	20 mg	15 mg	10 mg	5 mg	Pla
Stage 1	11	9*	11	11	12
Stage 2	61	61*	58	58*	55
Stage 3/4	15	16	16	14	16
Stage REM	12*	14*	15	16	17

* p <.05, two-tailed, vs pooled placebo.

10) Subjective assessments: Responses to the Morning Questionnaire tended to confirm PSG findings. sSL was not affected, but sTST improved for all doses of zolpidem except 5 mg. Quality of sleep was considered improved for Z5 and Z15 (2.1 for both, on a scale of 1-4), but not for Z10 and Z20.

11) Dose response: No analysis of dose response is included in the report.

12) Conclusions: The results of the study demonstrate the efficacy of zolpidem in a dose of 15 or 10 mg under the experimental conditions described above. Independent review by Biostatistics (HFD-713) gave results that are in agreement with those of the sponsor.

7.2 Other Lorex Studies

In addition to Clin Pharm studies and the efficacy and safety trials described above, the sponsor conducted two dose ranging studies, a long-term safety study, and one dose-preference study. They are summarized here.

LSH02 This was a randomized, double-blind crossover study to determine the lowest pharmacologically active dose of zolpidem in healthy male subjects, as well as dose-related effects on hypnotic activity, sleep staging, and efficiency. Safety, tolerance, and residual effects were also evaluated. Each of six study periods consisted of three consecutive nights in the sleep laboratory, with a three-day washout between periods. Subjects received 2.5, 5, 7.5, 10, or 20 mg of zolpidem or placebo on the first two nights, and placebo on the third. Investigator was T Roth, Henry Ford Hospital, Detroit.

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A total of 17 subjects, ages 22-35 yrs, was enrolled; 12 completed the crossover. Latency to persistent sleep decreased in a linear fashion with increasing dose, with an effect apparent at 5 mg (p=.003). There was a decrease in REM at 20 mg (p <.05). *[Synopsis - Vol 1.53/0014; full report -Vol 1.68]*

LSH11 This was a randomized, double-blind study consisting of two independent crossovers to evaluate the effects of zolpidem in doses of 5-20 mg on healthy elderly subjects. Each of three study periods (5 mg vs 15 mg vs pla; 10 mg vs 20 mg vs pla) consisted of three consecutive nights in the sleep laboratory, with a four-day washout between periods. Subjects received 5, 10, 15, or 20 mg of zolpidem or placebo on the first two nights, and placebo on the third. Investigator was M Scharf, Mercy Hospital, Cincinnati.

A total of 80 subjects, ages 60-79 years, was enrolled, of whom 35 were randomized; 33 completed the crossover. Data from 30 subjects were evaluable. All doses of active improved PSG latency and sleep efficiency (p ≤.008). REM sleep was decreased by the 10 and 20 mg doses (p <.05) but not the 5 and 15 mg doses *[Synopsis - Vol 1.53/0016; full report - Vol 1.80]*

LSH01 This was a randomized incomplete block pilot preference study in which patients received two doses of zolpidem. Study was double-blind with respect to doses but had no placebo control. Investigator was M Weintraub, Rochester, NY.

Hospitalized patients (N=14) were assigned to one of eight dose sequences (10-30, 10-40, 20-30, 20-40, 30-10, 30-20, 40-10, 40-20 mg). Efficacy was assessed by means of a sleep questionnaire and self-rating scales on the morning following each dose. A preference questionnaire (dose 1 vs dose 2) was completed on the morning after the second dose. No single dose emerged clearly superior to the others in terms of patient preference. *[Vol 1.67/0004]*

LSH12 This was a single-blind multicenter study to evaluate the safety of zolpidem 15 mg given daily for 12 weeks. Dose could be reduced to 10 mg at the discretion of the investigator. One-week placebo phases preceded and followed active treatment. There were no efficacy assessments. Five investigators participated; a total of 233 outpatient insomniacs were enrolled, of whom 155 (67%) completed study. *[Vol 1.84/0009]*

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7.3 Studies

The efficacy data from the LERS development program are not included in the NDA.

7.4 Lorex Trials Underway at Time of NDA.

LSH10/multicenter. 7-night SL study in chronic insomniacs. Initiated 12/86. (N=86)
LSH18/multicenter. 2-night SL study in volunteers. Initiated 10/87. (N=6)
LSH20/Dement. 4-night SL study in elderly insomniacs. Initiated 9/88. (N=2)
LSH60/Kryger. 7-night SL study in chronic insomniacs. Initiated 10/88. (N=2)

7.5 Lorex Trials Begun After Submission of the NDA.

LSH21/multicenter. 28-night OP study in elderly insomniacs. Initiated 10/89. (N=300).
LSH23/Dement. SL study of Z vs Triazolam in healthy normals. (N=18).
LSH24/multicenter. Dose response in elderly insomniacs. Initiated 9/89. (N=24).
LSH26/multicenter. 28-night SL study of rebound. (N=90).
LSH29/multicenter. 7-night OP study in short-term insomnia. Initiated 12/89. (N=20/center x 6).
LSH30/Dement+Roth. Single dose memory vs Tr vs Pl. Initiated 2/90. (N=20).
LSH61/multicenter (Canada). 4-night SL study in chr insomniacs. Initiated 7/89. (N=140)
LSH62/multicenter (Canada). 1-night study in hosp pts. Initiated 12/89. (N=312)
LSH63/one center (Canada). 16-night DB study vs placebo in pts w/ fibrositis. Initiated 1/91. (N=30)
LSH64/multicenter (Canada). 4-night XO sleep lab study in COPD pts. Initiated 3/90. (N=12/site)
LSH91/one center. Open-label single-dose crossover to establish bioequivalence. Initiated 2/91. (N=30)

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7.6 Overall Conclusions re: Efficacy.

The four Lorex efficacy trials provide statistical evidence strongly supportive of the efficacy of zolpidem as an hypnotic agent in adults with insomnia. Doses of zolpidem of 7.5 and 10 mg appear to provide significantly better response for most efficacy variables than does placebo in insomnia; doses of 10 and 15 mg are effective in insomnia.

Sleep lab demonstration of first night efficacy in inducing and maintaing sleep in insomniacs. SL decreased from min with Z15; from min with Z10. SE increased from % with Z15; from % with Z10. Effects persisted through 35 nights of active treatment. Subjective assessments showed a first night effect on sSL and sNA with Z15; sTST increased from min by the third week. Z10 improved sSL on the third week, sTST on the 4th week. No evidence of withdrawal/rebound insomnia.

Outpatient trial in chronic insomniacs showed a first week effect on all principal efficacy parameters with both Z15 and Z10. sSL decreased from min on Z15 and from on Z10. sTST increased min on Z15; min on Z10; sNA declined with both doses. Both doses maintained efficacy throughout treatment. No evidence of withdrawal or rebound.

"First night" study of insomnia in the sleep lab showed substantial difference between both actives (Z10 and Z7.5) and placebo on all three principal efficacy parameters. sSL and Sleep quality also improved.

Single-dose sleep lab study of the effects of a 3-hr phase advance showed an improvement in WTDS for Z20 and Z10; SE was increased with Z15 and Z5. Effects appear to be limited to the first 4 hrs of sleep. SL and NA were not affected.

It is concluded that zolpidem has been shown to be effective in the management of insomnia in doses of 5-20 mg under the conditions described in the studies under review.

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8.0 Safety Findings

8.1 Deaths

There were no deaths in the Lorex program.

There were nine deaths among patients participating in trials sponsored by LERS. Five deaths occurred during treatment with zolpidem and were reported to the IND. Following is a line listing of these patients. (Last column indicates location of CRF.)

Study	Pt	Age/sex	Rx/dose	Duration[a] of Rx	Concom Rx	Cause of death	Vol
Linden/ IIIGE01	08	82/F	Z20 Z10	4d 7d	Madopar Naftidrofuryl	Influenza Br pneumonia Card arrest	.352
Maarek/ IIIFR11	11-5	77/M	Z10 Z20	2d 23d	Amodiarone Enalapril Theophylline Digoxin Isosorbide	Pulm edema Renal f'lure CVA	.353
Roger/ IIIFR08	11	83/F	n/a	330d	Josamycin Digoxin	Pneumopathy Card decomp	.356
Roger/ IIIFR08	15	87/F	Z20 Z10	58d 210d	Mianserin P'barbital Amoxicillin P'midic acid NaCl Josamycin Amph'ricin B Rehydration	Gradual det'ration after b'pulm infection accompanied by oral candidiasis	.357
Roger/ IIIFR18	515	98/F	Z5	16d	Calciparine	Acute circulatory failure	.358

[a] Duration of treatment at the time of event leading to death; where two treatment durations are indicated, treatment was sequential and total duration to event onset is the sum of the two durations.

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Four additional deaths occurred but were not reported to the IND. As shown in the following line listing, two patients had recently completed a course of treatment with zolpidem.

Study	Pt	Age/sex	Rx/dose	Duration of Rx	Concom Rx	Cause of death	Vol
Coupez/ IIBE01	26	64/M	Placebo	1d	Digoxin Prednisolone	Pulm emb'm	.343
Received 1 dose of placebo; died 14 days later.							
Emeriau/ IIFR05	10	83/F	Z5 Z10 no drug	2d 4d 1d	Digitalin Fluidione Tamarine Naftidrofuryl Heparin	M'card inf'n	.346
Died 24 hrs after d/c zolpidem.							
Emeriau/ IIIFR10	201	99/F	FNZ1	22d	Spir'tone Dox'cline Amineptine Amoxicillin Cefatoxamine	Bronchial carcinoma w/ pneumonia	.346
Aspirated while in treatment w/ FNZ; died 3 hrs later.							
Shaw/ IIGB10	12	78/M	Z10 Plac	21d 2d	Navidrex Thioridazine Ampicillin	Pneumonia	.359
Died 48 hrs after d/c zolpidem.							

The submission includes narrative summaries of the clinical histories of these nine patients *[Vol 1.54/0128-0132]*. On review of these summaries and the CRFs, it appears that none of the deaths was related to treatment with study drug.

A child, not participating in a clinical trial, was found at autopsy to have serum levels of both zolpidem and triazolam; the case is the subject of a criminal investigation.

8.2 Overdose Experience

Included in the submission are summary reports by LERS of the clinical course of three patients, not participating in clinical trials, who overdosed on zolpidem.

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16 y/o male. Ingested 30-100 mg zolpidem plus tetrazepam and a third (unspecified) drug. Somnolent on admission. Recovered after gastric lavage.

46 y/o female. Ingested 400 mg zolpidem plus alcohol. Recovered after gastric lavage.

41 y/o female. Ingested 200 mg zolpidem plus alcohol. Admitted in Stage II coma. Recovered after gastric lavage and IV fluids.

Post-marketing experience reported at the time of submission included 26 cases of overdose. The sponsor's line listing of these cases shows doses of 40-400 mg. *[Table I, Vol 1.66/0017]* Symptoms varied from deep sleep to light coma, the latter occurring primarily when zolpidem was taken concomitantly with other drugs. One patient required respiratory assistance. All patients recovered uneventfully.

8.3 Significant Events Considered Possibly, Probably, or Definitely Drug-Related

a) A total of 111 subjects (zolpidem 77, active 23, placebo 10, unknown 1) withdrew from -sponsored clinical trials because of one or more adverse effects, an intercurrent illness, or both. The distribution of events that led to withdrawal, by body system and treatment group, is shown below.

	Zolpidem	Active	Placebo	Total
N patients d/c	77	23	10	111[a]
CNS+Periph	73	13	6	94[b]
Psychiatric	25	11	0	36
GI	17	10	4	31
Body as a whole	14	3	1	18
Cardiovascular	7	0	1	8
Respiratory	4	1	1	6
Other	17[c]	5	2	24

[a] Treatment unknown for one patient.
[b] Treatment unknown for one patient (2 events).
[c] Includes: autonomic (3), metabolic (1), musculoskeletal (1), myo-, endo-, pericardial and valve (2), skin and appendages (0), special senses (1), urinary system (2), vascular (2), vision (2), and lab (3).

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Included in this tabulation are the seven patient deaths occurring during or immediately after zolpidem that are discussed under **8.1 Deaths**; and 1 patient (**Hamdy/IIGB08 - 004**) discussed under **8.5.2 Clinical Laboratory Findings.**

On review of the narrative summaries for all patients who discontinued, it appears that 62/77 zolpidem patients discontinued because of adverse effects reasonably attributable to study drug; 37/62 (60%) were receiving doses ≥20 mg. The following line listing is stratified by dose; patients are listed by decreasing age. (Last column indicates location of narrative summary in Vol 1.65.)

Invest'r/Study	Pt Age/Sex	Reason for d/c	page
40 mg			
Ferreri/IIIFR01	64/F	Asthenia, vertigo, palpitations	*0171*
Ferreri/IIIFR01	18/F	Asthenia, depression	*0175*
35 mg			
Kummer/IIGE02	66/F	Daytime drowsiness	*0183*
30 mg			
Laxenaire/IIFR06	72/M	Confusional episode	*0185*
20 mg			
Roger/IIIFR08	100/F	Confusion, somnolence, aggressive behavior	*0225*
Emeriau/IIIFR10	92/M	Daytime drowsiness	*0153*
Emeriau/IIIFR10	82/M	Falls	*0157*
Shaw/IIGB10	83/F	Agitation, drowsiness	*0239*
Roger/IIIFR08	82/F	Anaphylactic shock	*0224*
Shaw/IIGB10	32/F	Lethargy, drowsiness	*0245*
Liebau/IIIGE002	78/F	Circulatory collapse, confusion, amnesia	*0187*
Hamdy/IIGB08	75/F	Nocturnal urinary incont'nce	*0178*
Liebau/IIIGE002	72/F	Nausea, vomiting, amnesia	*0192*
Shaw/IIGB10	72/F	Irritability, aggression	*0242*
Maarek/IIIFR11	71/F	Nausea, pseudo-vertigo	*0202*
Coupez/IIBE01	68/M	Nightmares, vertigo, loss of memory	*0129*
Dupuy/IIIFR07	63/M	Drowsiness, GI distention	*0145*
Coupez/IIBE01	62/F	Fall, nightmares	*0130*

- cont'd -

Invest'r/Study	Pt Age/Sex	Reason	page
20 mg - cont'd			
Wheatley/IIIGB01	60/F	Morning hangover, dizziness	*0257*
Dupuy/IIIFR07	59/F	Headache, nightmares, daytime drowsiness, lassitude	*0136*
Dupuy/IIIFR07	59/F	Constipation	*0148*
Wheatley/IIIGB01	58/F	Headache, dizziness	*0260*
Dupuy/IIIFR07	56/F	Headaches, heavy-headedness	*0146*
Ferreri/IIIFR01	53/F	Anxio-depressive symptoms, insomnia	*0164*
Ferreri/IIIFR01	50/F	Nausea, dizziness	*0162*
Ferreri/IIIFR01	48/F	Headache, dizziness, depressive state	*0176*
Maarek/IIIFR11	48/F	Feeling of drunkenness, anxiety, headache, difficulty awakening, hyperglycemia	*0209*
Wheatley/IIIGB01	45/F	Slept too deeply, hangover	*0170*
Dupuy/IIIFR07	39/M	Fatigue, asthenia, nausea, empty-headedne	*0137*
Ferreri/IIIFR01	34/F	Difficulty awakening, somnolence	*0166*
Ferreri/IIIFR01	34/F	Daytime somnolence	*0167*
Ferreri/IIIFR01	28/M	Hallucinations	*0169*
Ferreri/IIIFR01	26/F	Somnolence, amnesia	*0161*
Ferreri/IIIFR01	24/F	Anxiety, depressive state	*0170*
Dupuy/IIIFR07	21/F	Sleep disturbance, difficulty waking	*0133*
Wheatley/IIIGB01	n/a	Daytime fatigue	*0254*
Wheatley/IIIGB01	n/a	Headache	*0258*
10 mg			
Roger/IIIFR08	91/M	Persistent falling episodes	*0227*
Maarek/IIIFR11	85/M	Dry mouth, confusion	*0203*
Roger/IIIFR08	84/F	Disorientation, agitation, loss of vigilance	*0229*
Shaw/IIGB10	83/F	Drowsiness, ataxia	*0240*
Hamdy/IIGB08	79/F	Sedation	*0181*
Maarek/IIIFR11	75/F	Poor sleep, nightmares	*0204*
Maarek/IIIFR11	75/M	Malaise, fall, fixed expression, amnesia	*0206*

- cont'd -

Invest'r/Study	Pt Age/Sex	Reason	page
10 mg - cont'd			
Dupuy/IIIFR07	74/F	Chest tightness, tachycardia, trembling	*0141*
Hamdy/IIGB08	73/F	Daytime drowsiness	*0180*
Liebau/IIIGE002	71/F	Confusion, fall, retrograde amnesia	*0188*
Maarek/IIIFR11	66/F	Vertigo, drowsiness	*0208*
Maarek/IIIFR11	60/F	Cramps, nausea, malaise, syncope	*0205*
Liebau/IIIGE002	59/F	Amnesia, loss of appetite, peripheral neuropathy	*0191*
Maarek/IIIFR11	59/F	Double vision, gastralgia	*0210*
Wheatley/IIIGB01	56/M	Nausea, vomiting, giddiness	*0259*
Dupuy/IIIFR07	54/F	Dizziness, nausea	*0140*
Maarek/IIIFR11	54/M	Feelings of drunkenness and strangeness, diplopia, loss of memory	*0200*
Valla/IIFR02	53/F	Dry mouth	*0251*
Dupuy/IIIFR07	47/F	Trembling, lightheadedness, tachycardia,	*0142*
Liebau/IIIGE002	46/M	Headache	*0193*
Dupuy/IIIFR07	45/M	Vomiting, headache, hypotension, drowsiness	*0138*
Maarek/IIIFR11	41/F	Vertigo	*0207*
Dupuy/IIIFR07	25/F	Daytime drowsiness, pseudo-inebriation	*0134*
Dupuy/IIIFR07	18/F	Nightmares, daytime fatigue	*0144*
Wheatley/IIIGB01	n/a	Depression	*0261*

Despite the great age of some of these patients - 25/62 (40%) were >65 yrs of age - and the high doses, the reported adverse experiences were similar to those of younger people. None of the events was life-threatening and none required treatment; all patients recovered.

Four patients experienced falls:

Emeriau/IIIFR10 - This 82-yr old male fell twice: once on the 2nd and again on the 4th nights of zolpidem 20 mg; each time he was found in the morning asleep but uninjured. *[CRF at Vol 1.346/0319]*

- cont'd -

Coupez/IIBE01 - This 62-yr old female sustained a 3 cm laceration on the head when she fell approx 2 hrs after receiving a single dose of zolpidem 20 mg; suturing was required. The next morning the patient had no memory for the fall, but complained of nightmares. *[CRF at Vol 1.343/0139]*

Roger/IIIFR08 - This 91-yr old male fell during an episode of ambulatory wakefulness on the 7th night of zolpidem 20 mg but was unharmed. Dose was then reduced to 10 mg. Two more falls occurred after 17 and 19 nights. Medication was stopped after 44 nights. *[CRF at Vol 1.356/0191]*)

Maarek/IIIFR11 - This 75-yr old diabetic male fell approximately 30 min after receiving zolpidem 10 mg and had amnesia for the episode. Post-trauma blood work (not done by investigator) was reported to show his diabetes to be in good control. *[CRF at Vol 1.353/0160]*

Four female patients, ages 47-74 yrs, experienced symptoms referable to the cardiovascular system. In each case these symptoms appear to have been secondary to the sedative action of zolpidem.

Liebau/IIIGE002 - This 78 y/o pt fainted 30 min after first dose of zolpidem 20 mg and was withdrawn. *[CRF at Vol 1.351/0053]*

Ferreri/IIIFR01 - This 64 y/o pt reported asthenia, vertigo, and palpitations on Day 29 of zolpidem 20 mg. At discontinuation on Day 35 pt was found to have taken lorazepam 3.5 mg and nitrazepam 5 mg nightly, in addition to zolpidem. *[CRF at Vol 1.347/0318]*

Dupuy/IIIFR07 - This 74 y/o pt complained of tachycardia, a feeling of thoracic oppression, and trembling of the limbs after the first night of zolpidem 10 mg. Barbiturates were given for tremor; pt continued in study an additional 7 nights. No AEs reported at time of discontinuation. *[CRF at Vol 1.345/0080]*

Dupuy/IIIFR07 - This 47 y/o pt complained of depression, lightheadedness, trembling, tachycardia, asthenia, and insomnia at day 14 of zolpidem 10 mg and discontinued. No followup. *[CRF at Vol 1.345/0123]*

- cont'd -

Four additional patients, all female, had symptoms of clinical interest:

Roger/IIIFR08 - This 82-yr old pt awaiting nursing home placement was enrolled in a 6-mo open-label study of the use of zolpidem 20 mg in geriatric patients. Initial treatment was placebo x 3 nights. Concomitant medications were Dantron 25 mg (not in the PDR) and glycerine suppositories.

Approx 90 min after the first dose of active, the patient developed a generalized pruritic rash, with malaise and BP 70 mg Hg systolic. Dexamethasone was given IM (dose unknown) and the patient recovered. The patient had a similar episode 9 mo earlier after taking amoxicillin 2 mg/day for several days. Between these two occasions, she had received other medications (nitroglycerin, indalpine, naftidrofuryl, dihydroergotamine, paracetamol, and diethylsalicylamide) without incident. Investigator was "certain" the events were drug-related. This was probably an allergic or idiosyncratic response. Recovery without the use of aqueous epinephrine 1:1000 argues strongly against anaphylaxis. *[CRF at Vol 1.356/0002]*

Hamdy/IIGB08 - This 75 y/o pt being treated with zolpidem 20 mg nocturnal urinary incontinence, beginning on day 9, due to sleeping too soundly. Pt discontinued on day 14. *[CRF at Vol 1.350/0003]*

Maarek/IIIFR11 - This 48 y/o pt complained of feeling drunk, anxiety, headache, and difficulty awakening after zolpidem 20 mg x 3 days. Treatment continued for 30 days. Hyperglycemia (7.6 mmol/L), noted at baseline, was unchanged. *[CRF at Vol 1.353/0234]*

Liebau/IIIGE02 - This 59 y/o pt complained of amnesia, loss of appetite, and peripheral neuropathy (not described) after 29 days of treatment with zolpidem 10 mg. Symptoms resolved within 10 days. Pt d/c on day 42. *[CRF at Vol 1.351/0115]*

b) There were 66 discontinuations in the Lorex program, including 4 from **LSH10** (on-going; treatment remains blinded). The distribution of events that led to withdrawal of the remaining 62 pts, by body system and treatment group, is shown below. Included in the tabulation are the two patients discussed under **8.5.2 Clinical Laboratory Findings.**

- cont'd -

	Zolpidem 10	15	20	40	Placebo	Total
N patients d/c	12	36	2	2	10	62
CNS + Periph	10	22	2	1	1	36
Psychiatric	4	6	0	0	3	13
GI	2	12	2	0	0	16
Body as a whole	0	11	1	0	3	15
Liver/biliary	0	4	0	0	0	4
Other[b]	2	15	0	1	9	27

[b] Includes: autonomic (2), cardiovascular (2), endocrine (0), hearing/vestibular (0), heart rate/rhythm (1), musculoskeletal (1), resistance mechanisms (2), respiratory (3), skin + appendages (2), trauma (3), urinary tract (1), vision (0), white cell (1).

A total of 36/52 patients discontinuing zolpidem were participating in **LSH12**, the long-term open-label study, as were 7 patients who discontinued during the placebo lead-in phase. Dosage for the zolpidem patients was: 15 mg, 29; 15 mg reduced to 10 mg, 6; 10 mg, 1. Dosage for the remaining 16 zolpidem patients was: 10 mg, 5; 15 mg, 7; 20 mg, 2; and 40 mg, 2.

On review of the narrative summaries and CRFs for these patients, it appears that 19/52 zolpidem patients (11/36 in **LSH12** and 8/16 in other Lorex studies) discontinued because of adverse clinical effects reasonably attributable to the actions of zolpidem. These were extensions of the pharmacologic actions of zolpidem, such as drowsiness, disorientation, difficulty concentrating, lack of coordination or ataxia, irritability, and depression or fatigue; or, like headache, nausea and vomiting, and malaise, were predictable pathophysiologic correlates of the use of hypnotics. The following line listing is organized by dose; patients are listed by decreasing age. (Last column indicates location of narrative summary in Vol 1.65.)

Study	Pt	Age/Sex	Reason for d/c	page
40 mg				
LSH03		25/M	Incoordination	*0103*
LSH14		31/M	Severe itching	*0117*
20 mg				
LSH03		28/M	Headache, malaise	*0103*
LSH11		64/F	Lightheaded, nausea/vomiting	*0103*

- cont'd -

15 mg			
LSH12/Mendels	25/F	Disoriented, double vision	*0105*
LSH12/Scharf	35/F	Emesis, memory loss, nausea, R-sided weakness, vivid dreams, hallucinations	*0107*
LSH12/Thorpy	33/M	Daytime drowsiness	*0113*
LSH12/Weiss	46/F	Heaviness in head, nausea, sluggish, tired	*0115*
LSH12/Weiss	33/M	Depression, lack of concentration	*0115*
LSH17/Roth	39/M	Dizzy, drowsy, nausea	*0117*
LSH17/Walsh	50/F	Oversedation	*0118*
10 mg			
LSH12/Thorpy	46/F	Daytime drowsiness	*0110*
LSH12/Weiss	49/M	Drowsiness	*0114*
LSH12/Weiss	58/M	Headache	*0115*
LSH12/Weiss	38/F	Stomach cramps	*0115*
LSH12/Weiss	60/F	Headaches	*0116*
LSH12/Weiss	47/M	Irritability	*0116*
LSH17/Walsh	46/M	Drugged, mental slowness	*0117*

One subject in Dr Jasinski's single-dose crossover study of abuse potential, **LSH14**, presented with unusual clinical findings.

> This 31 y/o male poly-drug user was discontinued after Z40 because of severe itching, visual and auditory hallucinations, stomach cramps, and loose stools. No erythema or urticaria was observed; vital signs were stable. Pt was treated with diphenhydramine HCl 50 mg x 3 doses with relief of symptoms, and withdrew from study. *[Narrative summary at Vol 1.65/0117; CRF in Vol 14 of 2/18/91 Amendment]*

There were no severe or life-threatening events. None of the events attributable to zolpidem required treatment; all patients recovered.

8.4 Significant Events Considered Not Drug-related

a) A total of 9 LERS patients discontinued zolpidem for reasons which, upon careful review of the CRFs, appear unrelated to study medication. (Last columns gives location of narrative summary in Vol 1.65)

- cont'd -

Invest'r/Study	Pt	Age/Sex	Reason	page
Dupuy/IIIFR07		32/M	Fear of becoming addicted	*0139*
Emeriau/IIIFR10		86/F	Supraventricular tachycardia	*0154*
Emeriau/IIIFR10		86/M	Myocardial infarction	*0156*
Ferreri/IIIFR01		31/M	Renal colic	*0159*
Liebau/IIIGE02		68/F	Diarrhea and weight loss	*0189*
Maarek/IIIFR11		61/F	Reason not given	*0201*
Pagot/IIIFR04		26/F	Reason not given	*0218*
Ruther/IGE01		23/M	Unwilling to continue	*0236*
Torhorst/IIGE01		38/F	Cerebral hemorrhage	*0248*

b) A total of 31/52 Lorex patients treated with zolpidem discontinued for reasons which, upon review of the CRF, appear not to be related to study drug. Events coded as trauma (eg, "back injury") were looked at in terms of possible over-sedation, but were determined to be unrelated to administration of study drug.

Study	Pt	Age/Sex	Reason for d/c	page
15 mg				
LSH12/Mendels		56 M	Chest pain	*0103*
		30 M	Morning sedation	*0104*
		(Poor control of diabetes)		
		29 M	High AST/ALT	*0104*
		(Reported at end of placebo phase)		
		40 F	Flu symptoms	*0105*
		55 F	URI + pneumonia	*0105*
		40 M	Flu symptoms	*0106*
		46 F	Esophageal spasms	*0106*
		46 F	Back injury	*0107*
Scharf		59 F	Indigestion	*0107*
		34 F	Tingling, numb in L arm	*0108*
		58 M	Stiff neck, tingling hands	*0108*
		36 F	Flu symptoms	*0109*
		41 F	Anxiety reaction	*0109*
		(Family difficulties)		
Thorpy		29 F	Hypothyroidism	*0109*
		56 M	Chest tightness	*0110*
		25 F	Migraine, flu symptoms	*0111*
		62 F	Labile hypertension	*0111*

- cont'd -

Study	Pt	Age/Sex	Reason for d/c	page
15 mg - cont'd				
		59 M	Hypertension	*0112*
	Weiss	51 M	ST segment abnormality	*0114*
		41 M	Urinary retention	*0114*
		56 F	Depression	*0114*
		(Personal problems)		
LSH17/Scharf		54 F	Stomach discomfort	*0118*
LSH19/Cohn		51 F	Chest, jaw, shoulder pain	*0118*
	Docherty	45 M	Anxiety	*0119*
		(Onset prior to entry)		
	Kann	54 F	Burning sensation on tongue	*0119*
	Leppick	45 F	Uncontrollable crying	*0121*
		(Menopausal)		
10 mg				
LSH12/Thorpy		58 F	Itching rash	*0113*
		(Pemphigoid lesions - onset prior to study)		
LSH12/Weiss		46 F	Back pain	*0116*
LSH19/Lahmeyer		31 M	Depression	*0120*
		(History of recurrent depression)		
	Leppick	54 F	Headache, dry mouth	*0120*
		(Flu, glucose intolerance)		
		56 M	Hypertension	*0121*

8.5 Other Findings

8.5.1 ADR Incidence Tables

Adverse events reported in this submission are defined by the sponsor as those treatment-emergent adverse events (TEAE) occurring on-therapy that a) were not present at baseline or, if present, worsened on therapy; and b) occurred within 24 hrs of dosing during active treatment. TEAE incidence rates were calculated for all Lorex-sponsored trials, including clinical pharmacology studies and uncontrolled safety/efficacy trials. Sponsor's list of TEAEs for all studies, classified by means of standard COSTART terminology, is at *Vol 1.59/0003*.

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In the clinical pharmacology studies, all of which involved daytime dosing, observed effects were recorded as "Signs and Symptoms"; those considered "serious" were recorded as TEAEs. These events were then added to the adverse event data base and are included in the summary tabulations of AEs. Sponsor's list of all "Signs and symptoms" is located at *Vol 1.59/0021*.

The sponsor has summarized incidence rates for adverse effects reported for zolpidem patients in the Lorex development program for all studies and for the six controlled sleep studies, ie, single-dose studies in healthy normals; **LSH02** and **LSH11**, two-dose crossover studies, also in healthy normals (age ranges yrs, respectively); and 35-night sleep lab and 31-night outpatient studies, respectively, in insomniacs. As shown in the table below, the most common TEAEs in all studies and in all controlled studies were CNS-related:

	All studies	Controlled sleep studies
N	940	576
Any TEAE	45.2%	24.1%
Drowsiness	13.8%	5.6%
Headache	12.9%	8.0%
Dizziness	6.4%	2.8%
Nausea	6.2%	3.3%
Lightheadedness	5.7%	1.4%
Fatigue	5.2%	-

These data are not apprcpriate for labelling purposes, however, since they combine data from one- and two-night studies with data from 31- and 35-night studies. The studies are also disparate in size, five of the six having zolpidem populations of 12-87 subjects and one, having 360 zolpidem subjects. The latter study, being concerned with the effects of zolpidem on healthy subjects with insomnia (albeit laboratory-induced), provides the best model for predicting clinical toxicity.

The following table summarizes the TEAE experience for by dose. Note that all of the most common TEAEs were reported in this study. At doses ≤10 mg, only headache and nausea occurred with an incidence ≥1%.

- cont'd -

	≤15 mg N=102	≥10 mg N=258	Placebo N=102
Any adverse effect:	25 (24.5%)	14 (5.4%)	8 (7.8%)
Central/Periph Nerv Syst:			
headache	10 (9.8%)	6 (2.3%)	6 (5.9%)
confusion	3 (2.9%)	1 (0.4%)	-
dizziness	2 (2%)	1 (0.4%)	-
lightheaded	2 (2%)	1 (0.4%)	-
ataxia	2 (2%)	-	-
drowsiness	1 (1%)	1 (0.4%)	-
dysphasia	1 (1%)	-	-
drugged	1 (1%)	-	-
diff concentrating	-	1 (0.4%)	1 (1%)
lethargy	-	-	1 (1%)
Vision:			
vision abnormal	2 (2%)	-	-
diplopia	1 (1%)	-	-
eye irritation	1 (1%)	-	-
Body as a whole:			
fatigue	1 (1%)	-	-
GI:			
nausea	5 (4.9%)	3 (1.2%)	-
vomiting	2 (2%)	1 (0.4%)	-
diarrhea	1 (1%)	1 (0.4%)	-
dyspepsia	1 (1%)	-	-
anorexia	1 (1%)	-	-
gingival bleeding	-	-	1 (1%)
Psychiatric:			
agitation	1 (1%)	-	-
amnesia	1 (1%)	-	-
emotional lability	1 (1%)	-	-
Musculoskeletal:			
myalgia	-	1 (0.4%)	-
Respiratory:			
pharyngitis	-	1 (0.4%)	-
dyspnea	-	1 (0.4%)	-
Hearing/vestibular:			
tinnitus	-	1 (0.4%)	-
Totals	40 (39.2%)	20 (7.8%)	9 (8.8%)

There were 9 reports of amnesia after treatment with zolpidem in Lorex controlled studies; none, after placebo. Typically, these were single events of morning forgetfulness, generally mild; no patient discontinued; dose was not changed.

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As shown in the following tabulations, amnesia was both dose- and age-related.

Dose	TEAE (%)
5 mg	0/97 (0%)
10 mg	2/218 (0.9%)
15 mg	3/152 (2.0%)
20 mg	4/95 (4.2%)

Age	TEAE (%)
≤24 yrs	1/187 (0.5%)
25-49 yrs	5/280 (1.8%)
≥50 yrs	3/109 (2.8%)

The following TEAEs were reported in other Lorex controlled trials with frequencies Z>P.

	Zolpidem N=576	Placebo N=256
Autonomic		
dry mouth	5 (0.9%)	1 (0.4%)
Body as a whole		
allergy	3 (0.5%)	0
chest pain	2 (0.3%)	0
flu-like symptoms	2 (0.3%)	0
rigors	1 (0.2%)	0
edema	1 (0.2%)	0
Central/peripheral nervous system		
dreaming abnormal	2 (0.3%)	0
dysarthria	2 (0.3%)	0
vertigo	2 (0.3%)	0
decreased cognition	1 (0.2%)	0
hypoaesthesia	1 (0.2%)	0
sleep disorder	1 (0.2%)	0
GI system		
constipation	1 (0.2%)	0
flatulence	1 (0.2%)	0
gastritis	1 (0.2%)	0
Heart rate and rhythm		
palpitation	1 (0.2%)	0
Psychiatric		
anxiety	2 (0.3%)	0
panic attack	1 (0.2%)	0
hallucination	1 (0.2%)	0
hysteria	1 (0.2%)	0
Resistance mechanisms		
infection	1 (0.2%)	0
infection, fungal	1 (0.2%)	0
lymphadenopathy	1 (0.2%)	0

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	Zolpidem N=576	Placebo N=256
Respiratory system		
sinusitis	7 (1.2%)	2 (0.8%)
bronchitis	1 (0.2%)	0
laryngitis	1 (0.2%)	0
Skin and appendages		
rash	1 (0.2%)	0
Special senses		
taste perversion	3 (0.5%)	0
Urogenital		
urinary tract infection	4 (0.7%)	1 (0.4%)
cystitis	1 (0.2%)	0
micturition disorder	1 (0.2%)	0

A total of 22 TEAEs were reported more often with placebo than with zolpidem. These are listed in **Appendix G.**

8.5.2 Clinical Laboratory Findings

Clinical laboratory data were obtained at pre- and post-dose visits in 21/30 LERS and 14/16 Lorex trials, yielding a sample of approximately 1,496 zolpidem-treated patients with at least some laboratory data. Tables in the next two sections provide proportions of patients in the pool of zolpidem studies meeting arbitrarily defined criteria for changes in laboratory values of possible clinical significance. LERS patients with laboratory PCSAs are listed in sponsor's 2/26/91 submission; Lorex patients are listed at **Appendix H.**

8.5.2.1 Clinical Chemistry

The following table provides criteria for identifying patients with changes from baseline of possible clinical significance. Only those patients who were relatively normal at baseline and who then exceeded these criterion values on assigned treatment are counted:

Chemistry	High	Low
BUN	≥30 mg/dl	---
Creatinine	≥2 mg/dl	---
Total Bilirubin	≥2 mg/dl	---
Alkaline Phosphatase	3 X ULN (U/L)	---
SGOT and SGPT	3 X ULN (U/L)	---
Uric Acid (Males)	≥10.5 mg/dl	---
Uric Acid (Females)	≥8.5 mg/dl	---

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The following table *[3/6/91 submission]* provides the actual proportions (n/N, where n = the number of patients exceeding criterion values in the direction of interest while on drug and N = number of patients not exceeding criterion values at baseline):

	LERS		Lorex	
	Zolpidem	Placebo	Zolpidem	Placebo
BUN	0/9	1/63	3/513	-
Creatinine	1/222	0/58	2/464	-
Tot Bilirubin	0/210	0/62	5/510	-
AST	2/216	0/54	1/515	-
ALT	3/221	0/51	3/495	-
Uric acid	0/8	1/46	1/449	-

Three patients (LERS 1, Lorex 2) had abnormal chemistries:

Hamdy/IIGB08 - This was a 90-yr old white female (5', 106#) participating in a short-term DB study vs placebo. Other dx: congestive heart failure, osteomalacia, infected ulcer L leg. Baseline labs were WNL except for WBC 12.1 x 10^3 (range and BUN 9.6 (range 3-7). Patient received zolpidem 20 mg x 10 doses and was then discharged from hospital. Labs at discharge were again within normal limits except for WBC 2.5 and alk phos 196 U/L. *[Vol 1, 2/26/91 Amendment]*

LSH12/Mendels - This was a 34 y/o black male (5'1", 170#) with a history of hepatitis B and poly-drug use. Baseline labs included WBC 11.1 x 10^3, with 1,220 (11%) monocytes. Zolpidem 15 mg was begun 7/28. Serial labs were as follows: (values WNL not shown):

	7/16	7/28	8/5	8/13	8/26	9/8	9/22	9/25	9/29	10/7
Bili (0.2-1.2)	-	1.4	1.4	-	-	-	-	-	-	-
ALT (6-43)	-	-	-	-	80	53	85	83	76	55
AST (11-36)	-	-	-	38	53	-	65	109	80	60
WBC (4.4-10.7)	11.1	11.4	12.4	11.1	-	-	-	-	-	-
Neut (2.0-7.2)	-	8.1	8.2	7.8	-	-	7.8	-	-	-
Mono (0.1-0.9)	1.22	-	-	-	-	-	-	-	-	-

- cont'd -

The patient discontinued treatment on 9/25 (day 60). Followup labs two wks later showed liver function returning to normal. *[Vol 7, 2/18/91 Amendment]*

LSH19/Leppik - This was a 30 y/o obese white male (70", 246#) participating in the 31-day outpatient study of the use of zolpidem 10/15 mg in insomnia. The patient had a history of allergies to dust and pollen and had undergone cholecystectomy one month prior to enrollment. Pre-study labs (12/22/87) were unremarkable; ALT=46 (6-43 U/L), AST=16 (11-36 U/L). On the first day of study the patient consumed 5 glasses of beer; a week later, he had a flu-like illness, with headache, fatigue, stomach ache, diarrhea, and decreased appetite. The patient self-medicated with Kaopectate 2 tablets and the condition cleared up. He then decided to begin taking one five grain aspirin a day, to prevent heart attacks, and continued this regimen for the remainder of the study. During the second week of the study the patient (whose home was in Minneapolis) took a vacation to Reno, Nevada; in the third week, to Las Vegas. Exit labs (2/18/88) were again within normal limits, except for ALT=146 and AST=79. Repeat labs were done on 2/23: ALT=46, AST=42. *[Vol 26, 2/18/91 Amendment]*

8.5.2.2 Hematology

The following table provides criteria for identifying patients with changes from baseline of potential clinical significance. Only those patients who were relatively normal at baseline and who then exceeded these criterion values at some time on assigned treatment are counted for the proportion table that follows.

Hematology Variables	Criterion values High	Low
Hemoglobin (Males)	18.5 g/dl	≤11.5 g/dl
Hemoglobin (Females)	16.5 g/dl	≤9.5 g/dl
Hematocrit (Males)	55%	37%
Hematocrit (Females)	50%	32%
White Blood Cells	≥16 X $10^3/mm^3$	≤2.8 X $10^3/mm^3$
Eosinophils	≥10%	----

- cont'd -

The following table provides the actual proportions (n/N, where n = the number of patients exceeding criterion values in the direction of interest while on drug and N = the total number of patients not exceeding criterion values at baseline):

	LERS		Lorex	
	Zolpidem	Placebo	Zolpidem	Placebo
Hemoglobin	6/224	0/58	1/506	-
Hematocrit	6/219	2/58	7/493	-
WBCs	1/224	0/58	3/501	-
Eosinophils	5/222	0/3	7/486	-
Platelets	1/221	0/46	0/46	-

Three Lorex patients had hematologic abnormalities:

LSH12/Mendels - This was a 26-yr old bisexual black male participating in the 12-wk safety study of zolpidem 15 mg. The patient gave a history of being allergic to paregoric; stated that he had had a vasectomy; and had smoked 2 cigarets/day for the past year. He began the trial 6/15 with WBC 4.43 x $10^3/mm^3$, with 63% polys and 29% lymphs. WBCs decreased to 3.58 by the end of the placebo lead-in, and continued to decrease over the next two weeks, as follows:

	6/15	7/01	7/10	7/16	7/27	8/04	8/07	8/10	8/31
WBC ($x10^3$)	4.43	3.58	3.81	2.91	3.08	2.80	4.55	4.80	5.20
% Poly	63	59	62	41	63	55	50	73	66
% Lymph	29	35	28	49	30	28	40	17	27

The patient felt well, and reported no adverse effects, but was discontinued from study on 8/4 because of the low white count. He was seen by a hematologist on 8/7 at the request of the investigator, and was found to have an unspecified medical illness which confounded interpretation of the WBC count. Patient refused to release results of the consultation. *[Vol 7, 2/18/91 Amendment]*

LSH04/Cohn - This was a 28 y/o white male participating in a 4-period crossover study in which respiratory drive was assessed in subjects who received single doses of zolpidem 10 and 20 mg, codeine phosphate 60 mg, and placebo, in random order.

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The sponsor notes a post-treatment eosinophil count of 10% and states that no adequate explanation for this result can be found. Pre-treatment eosinophil count was 9%; all other pre- and post- CBC values show a similar correspondence. Review of the patient's case report shows that he was taking ampicillin 250 mg QID during the screening period. *[Vol 6, 2/18/91 Amendment]*

LSH14/Jasinski - This was a 34 y/o black male multiple-drug user participating in a DB randomized crossover study of abuse liability of zolpidem 10, 20, and 40 mg vs diazepam 10 and 20 mg vs placebo. Single doses of study medication were administered on consecutive days, with two-day drug-free screening period and one-day followup; subjects were domiciled on the clinical research ward during study. Pre-study values were: WBC 2.8 x 10^3/mm^3 (range: ; alk phos 155 (range: The patient experienced intermittent elevations of BP (diastolic to 102 mm Hg) on one day of study, but was otherwise free of complaints. Post-study values were: WBC 2.0, alk phosph 152. The investigator does not state an opinion about the lab results; the sponsor states that the low white count was "thought to be consistent with the patient's medical history". No followup was available. *[Vol 20, 2/18/91 Amendment]*

8.5.2.3 Urinalysis

The criteria for identifying patients with changes from baseline of potential clinical significance on the urinalysis variables of interest are as follows:

protein - 2 or above
glucose - 2 or above
casts - 2 or above

Only those patients who were relatively normal at baseline and who then exceeded these criterion values at some time on assigned treatment are counted. There were no discontinuations due to abnormal urinalysis.

None of the abnormalities described above was serious or accompanied by any clinical symptoms, and none could be clearly attributed to zolpidem. They are considered not drug-related.

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8.5.3 Vital Signs

Blood pressure and heart rate were measured pre-study or during the screening period in all Lorex trials, and were generally repeated pre-dosing. Body weights and temperatures were typically measured only pre-study; post-treatment BP/HR measurements were obtained in all studies. Of the 940 zolpidem patients, 329 had their BP measured in the standing position; 844, in the seated position; 306, in the supine position. Criteria for identifying vital signs as clinically significantly abnormal are as follows:

Systolic BP -	high:	180mm Hg, with 20mm increase from baseline;
	low:	90mm Hg, with 20mm decrease from baseline;
Diastolic BP -	high:	105mm Hg, with 15mm increase from baseline;
	low:	50mm Hg, with 15mm decrease from baseline;
Heart rate -	high:	120 bpm, with 15 bpm increase from baseline;
	low:	50 bpm, with 15 bpm decrease from baseline.

On average, vital signs were assessed 32.6 times in each zolpidem subject, and 25.5 times in each placebo subject. As shown in the following table, post-treatment PCSA vital signs were found in 10% of zolpidem patients and 12% of placebo patients.

	Z		Pla	
N	929		337	
N w/ PCSA	92	(10%)	40	(11.9%)
No. of Assessments	30,332		8,585	
No. of PCSA Assessments	202	(0.7%)	96	(1.1%)

PCSAs were equally divided between BP and HR. Frequency and direction of change of vital signs were not treatment-dependent. No pt exhibited standing systolic and diastolic BP and HR which,ds together, were consistent with orthostatic hypotension. PCSA findings are summarized in the following table:

	Z			Pla		
	Sys	Dia	HR	Sys	Dia	HR
Supine						
N	306	306	224	30	30	30
Assessments	3,146	3,145	1,464	391	391	391
PCSA	19	18	10	1	2	2
(% PCSA)	(0.6%)	(0.6%)	(0.7%)	(0.2%)	(0.5%)	(0.5%)
Sitting						
N	844	844	844	285	205	285
Assessments	4,724	4,725	4,721	1,727	1.727	1,723
PCSA	46	23	49	43	15	24
(% PCSA)	(1.0%)	(0.5%)	(1.0%)	(2.5%)	(0.9%)	(1.3%)

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	Z			Pla		
	Sys	Dia	HR	Sys	Dia	HR
Standing						
N	329	329	247	52	52	52
Assessments	3,241	3,238	1,928	750	750	735
PCSA	22	7	8	7	1	1
(% PCSA)	(0.7%)	(0.2)	(0.4%)	(0.9%)	(0.1%)	(0.1%)

8.5.4 ECG

ECGs were not done on LERS patients.

Pre- and post-study ECGs were obtained in 6/9 Lorex Clin Pharm studies; in **LSH11**, the dose-ranging trial in elderly subjects; and in **LSH12**, the long-term open-label safety study. N=517 subjects were assessed. One pt had post-treatment ECG abnormalities.

LSH12/Weiss - This was a 51 y/o male with a history of bacterial endocarditis and suspected mitral valve prolapse. Baseline ECG was normal. The patient had abnormal ECGs, with ST depression in leads V2-V5, six and eight weeks after beginning zolpidem 15 mg. The patient was discontinued from study; repeat ECG two days later continued to show ST segment depression. The consulting cardiologist felt that the findings were related to the subject's pre-existing cardiac condition; after review of the CRF, the present writer concurs in that judgment. *[Vol 1.337/0056]*

8.5.5 Special Studies

8.5.5.1 Effects on Respiratory Function

The effects of zolpidem on respiratory drive were assessed in healthy subjects in one safety and tolerance study and several studies in which ventilatory response to CO_2 challenge was measured by the non-rebreathing technique and by respiratory inductive plethysmography. Zolpidem 10 mg had no effect on respiratory drive; zolpidem 20 mg produced sleep and a minor reduction in mean inspiratory flow; no effect on ventilatory response to hypercarbia during wakefulness was observed.

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LSH03 This was a single-blind study of single morning doses of zolpidem 20-90 mg given to healthy subjects (N=15) in eight weekly sessions in increments of 10 mg/week. Continuous recording of PSG, oxygen saturation, respiratory rate, and ECG began 10 min before drug administration and continued until the subject was fully awake; minimum recording time was 4 hrs. Four subjects who received zolpidem 50 mg were recruited for an extra study session to receive 0.5 mg triazolam.

10/15 subjects completed the study; 4/10 completed all doses, with 6/10 discontinuing because of adverse effects. One subject complained of headache beginning 24 hrs after the 20 mg dose; a second subject experienced vomiting at 40 mg; two others, at 70 mg; the fifth subject was ataxic, dizzy, and confused at 70 mg; the sixth experienced confusion and agitation at 80 mg.

9/15 subjects receiving 20 mg experienced oxygen desaturation to 80-90%; 3/9 desaturated only while awake. There was no dose response with respect to number, intensity, or duration of desaturations. Cardiac and respiratory rates were not affected; PACs and PVCs occurred but were not dose-related. *[Vol 1.70/0001]*

Maillard/IFR27 "Effect of zolpidem on respiratory function in the healthy subject." This was a double-blind single-dose crossover trial of the effects of CO_2 challenge on respiratory response to zolpidem 10 and 20 mg vs diazepam 10 mg and placebo (N=16; 8 male, 8 female). No respiratory suppression was observed. Adverse effects of zolpidem 10 mg were: imbalance (3); asthenia and diplopia (1 each); adverse effects of zolpidem 20 mg were: imbalance (7), nausea (6), diplopia (4), headache and slurred speech (1 each). *[Vol 1.39/0002]*

LSH07 This was a pilot two-period study assessing effects of zolpidem 40 mg on respiratory inductive plethysmography and vital signs in healthy subjects responsive to codeine (N=8). Subjects were given codeine phosphate 60 mg and were then assessed for respiratory suppression by CO_2.

4/8 had at least a 30% reduction in the ventilatory response slope. Assessment of respiratory drive following zolpidem 40 mg in these 4 subjects was impractical because of sedation. Two subjects vomited; another subject experienced euphoria without sedation.

An additional six subjects were tested with zolpidem (3 with 10 mg and 3 with 20 mg), but not codeine. One subject had a 37% reduction in the linear regression for ventilatory response one hr after dosing with 20 mg. No TEAEs were reported. *[Vol 1.74/0001]*

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LSH04 This was a four-period crossover study to evaluate effects of single doses of zolpidem 10 and 20 mg on respiratory drive vs codeine phosphate 60 mg and placebo in healthy subjects (N=12). Respiratory inductive plethysmography (RIP) was assessed pre-dose and 1, 2, 3, 4 and 5 hrs after dosing; ventilatory response to CO_2 was assessed pre-dose and 1 and 3 hrs after RIP.

Zolpidem 10 mg had no effect on respiratory drive; the 20 mg dose produced sleep and reduced mean inspiratory flow but had no effect on ventilatory response during wakefulness. Four subjects reported adverse effects on placebo, 5 on zolpidem 10 mg and 11 on zolpidem 20 mg, and 1 on codeine. Common adverse effects were slurred speech, dizziness, pallor, lightheadedness and diplopia. Two subjects vomited, one at 10 mg and one at 20 mg. *[Vol 1.71/0001]*

LSH05 This was a pilot single-dose study in which 4/10 healthy subjects exhibited depressed ventilatory response to CO_2 at 1, 3, and 6 hrs after dosing with 60 mg codeine phosphate and were then retested with zolpidem 40 mg. One additional subject who did not show respiratory suppression after codeine was also tested. One of 5 subjects exhibited respiratory suppression after zolpidem: $PaCO_2$ increased 9% at 15 L/min alveolar ventilation in this subject after zolpidem, but 57% after codeine. Adverse effects included drowsiness and grogginess after codeine, and unsteadiness after zolpidem. *[Vol 1.72/0001]*

LSH06 This was a single-dose parallel-groups trial of the effects of CO_2 (2%, 4%, and 6%) challenge on respiratory response to zolpidem 20 mg (N=31) vs codeine phosphate 60 mg (N=29) vs placebo in healthy subjects (N=30). No respiratory suppression was observed. Adverse effects of zolpidem 20 mg were sleepiness (83%), visual disturbances (36%), and nausea and vomiting (10%). *[Vol 1.73/0001]*

8.5.5.2 Residual Effects

a) Rebound and carryover: Two Lorex trials, (35-night sleep lab) and (31-night outpatient), were designed with a post-treatment single-blind placebo observation period to detect changes in sleep patterns following abrupt discontinuation of treatment. There were no changes in latency or sleep efficiency on the first day off active treatment in . In there was slight evidence of decreased total sleep time on the first night after 31 nights of treatment with zolpidem 15 mg, but none in the 10 mg group.

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b) Psychomotor function: Tests were used to assess possible impairment of subjects in 2 LERS trials and 5 Lorex trials: 3 trials in healthy adult volunteers (**Simon/IFR29**, **Grilliat/IFR22**, and **LSH02**; two trials in insomnia ; in **LSH11**, a trial in elderly volunteers; and in a trial in insomniacs.

Tests used were the Digit Symbol Substitution Test, the Digit Symbol Copying Test, and reaction time; tests were generally administered 8-10 hrs after dosing.

There were no decrements in psychomotor performance after doses of zolpidem of 2.5 to 20 mg in adult volunteers after either phase shift or undisturbed sleep (**LSH02**, **Simon/IFR29**, and **Grilliat/IFR22**). In the 35-day study in insomniacs, there were no decrements in DSST scores with either 10 or 15 mg. After two nights of zolpidem 5 to 20 mg in healthy elderly volunteers in **LSH11**, DSST scores decreased 5-12% ($p < .05$).

In **LSH11**, tests of reaction time and motor coordination and patient ratings on visual analog scales indicated no residual effects at doses of 5-20 mg.

c) Daytime sleepiness: The Stanford Sleep Latency Test, administered 1 and 3 hrs after sleep in showed no impairment of healthy noninsomniac volunteers. A similar lack of daytime effect on healthy elderly volunteers was observed in **LSH11**.

d) Memory: As noted under **8.5.1 ADR Incidence Tables**, amnesia was reported by 9/576 subjects in the Lorex efficacy trials. Tests of memory function in **LSH11** found no evidence of a negative effect of zolpidem.

8.5.6 Drug-demographic Interactions

a) LERS conducted seven age/race interaction studies. None was found; no significant adverse effects occurred.

Colle/IFR44 "Nocturnal pharmacokinetics of zolpidem in children." This was a randomized DB parallel-groups study of single h.s. doses of zolpidem 10 mg vs placebo. N=12 otherwise healthy children 6-14 yrs of age undergoing evaluation for delayed growth participated. Zolpidem was absorbed at the same rate as in adults (t_{max}=1.3 ± 0.4 vs 1.8 ± 0.1 hrs) but cleared more rapidly (Cl=0.86 ± 0.1 vs 0.26 ± 0.03 L/hr/kg in adults). "Floating sensation" was reported by a 12-yr old girl. *[Vol 1.42/0002]*

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Thebault/IFR11 "Zolpidem: Safety and pharmacokinetics in middle-aged subjects." This was an open-label study of single morning doses of zolpidem 20 mg administered to N=8 healthy fasting volunteers 46-59 yrs of age. Kinetics were similar to those in younger subjects. Sedation was noted in all subjects. Two subjects reported diplopia; one subject experienced nausea and vomiting. *[Vol 1.42/0251]*

Kurtz/IFR38 "Zolpidem: Assessment of safety, pharmacokinetics, and sleep, following the administration of repeated doses to elderly subjects." This was a 7-night sleep lab study, with one placebo baseline night and two post-treatment placebo nights to observe withdrawal effects, if any. Subjects (N=12) were healthy volunteers 60-74 yrs of age.

Both kinetics and PSG parameters were similar to those in the general population. Respiratory tracings showed an increase in episodes of apnea during NREM sleep on the first drug night; incidence of apnea during REM sleep decreased over the course of the study. Dry mouth, reported for both zolpidem and placebo, was the only adverse effect. *[Vol 1.42/0147]*

Emeriau/IFR25 "Pharmacokinetics of zolpidem (20 mg) in the elderly subject." This was an open-label single-dose study in N=8 otherwise healthy subjects 70-85 yrs of age undergoing endocrine evaluation. The kinetic profile of zolpidem was somewhat altered: C_{max}, $t_{½}$, and AUC were increased; t_{max} was unchanged; there was no effect on FSH, LH, TSH, STH, or prolactin. There were no adverse events. *[Vol 1.42/0049]*

Lambert/IFR08 "Pharmacokinetics of zolpidem in the elderly subject." This was an open label study zolpidem 10 mg administered at 9 am to N=6 healthy volunteers 70-84 yrs of age. C_{max} was increased; other kinetic parameters were unchanged. All subjects exhibited sedation. *[Vol 1.42/0212]*

Forette/IFR34 "Pharmacokinetics of zolpidem in the elderly subject (IV vs oral)." This was an open-label study of single doses of zolpidem 10 mg administered orally and by slow infusion to subjects (N=9, 2 male, 7 female) who were 81-95 yrs of age. All subjects had significant medical disabilities but were not insomniac. T_{max} and absolute bioavailability were similar to those in a group of N=10 healthy volunteers 19-31 yrs of age who served as controls; all other kinetic parameters were increased: for example, C_{max} in the older subjects was 238.3 ± 34.9 vs 138.6 ± 11.7 in the young. No adverse events were reported. *[Vol 1.42/0098]*

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Vandel/IFR28 "Zolpidem: Pharmacogenetic study." This was a single-dose open-label study in which zolpidem 20 mg was given in the morning to four groups of 10 fasting volunteers 19-45 yrs of age: European, Maghreb (Arabs of NW Africa), Negro, and Asiatic. Kinetics were similar to those of the general population.

Sedation, measured on the Stanford Sleepiness Scale, appeared sooner and lasted longer in the Asiatic group, but the difference was thought due to lower body weight. Adverse effects were similar in all four groups, and were limited to those most frequently reported with zolpidem, ie, headache, diplopia, hiccup, nausea and vomiting, thirst, and dizziness. *[Vol 1.42/0291]*

b) The age- and dose-related increase in amnesia in Lorex's placebo-controlled sleep trials has been pointed out (See **8.5.1 ADR Incidence Table**). Nausea was the only other TEAE exhibiting both age- and dose-related increases.

Dose	D/C
5 mg	1/97 (1%)
10 mg	4/218 (1.8%)
15 mg	7/152 (4.6%)
20 mg	5/95 (5.3%)
Pbo	0/256

Age	D/C
≤ 24 yrs	5/187 (2.7%)
25-49 yrs	10/280 (3.6%)
≥ 50 yrs	4/109 (3.7%)

At doses of zolpidem of 10 mg or less, incidence rates for placebo exceeded those for both male and female patients on active. At higher zolpidem doses, TEAEs were twice as frequent among females (56.2%) as among males (23.4%); placebo rates were 28.9% and 10.7%, respectively.

c) The two Lorex dose-ranging studies evaluated safety in the general adult population and a population of elderly subjects. Older subjects were more likely than younger ones to experience morning-after drowsiness, but at doses of 10 mg or less this is not likely to be a problem. (See: **7.2 Other Lorex Studies**)

LSH02 This was a double-blind randomized study using a crossover design, with subjects 22-35 yrs of age (N=12) spending six 3-night periods in the sleep lab. Doses were 2.5-20 mg. Double-vision and slurred speech were reported twice during the period between dosing and bedtime, once at 10 mg and once at 20 mg. Adverse effects reported the next morning, all at 20 mg, included depression and difficulty concentrating (one each), and amnesia for the period between dosing and going to bed (3 occurrences).

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LSH11 This was a double-blind crossover study of the same design as **LSH02**. Doses of 5, 10, 15, and 20 mg were studied vs placebo. A total of 35 healthy volunteers 60-79 yrs of age were empanelled; data for 30 subjects were evaluable.

Commonest adverse event was headache (12% for both zolpidem and placebo), and was not dose-related. Morning drowsiness was the only other adverse effect reported more than once at any dose, and was dose-related: 6% at 5 mg, 13% at 10 mg, 24% at 15 mg, and 35% at 20 mg, vs 9% for placebo. There were no significant changes in vital signs or laboratory parameters.

8.5.7 Drug-disease Interactions

Zolpidem was studied in patients with a variety of illnesses: cardiorespiratory and hepatorenal disease; depression; and obesity. As described below, the study in depression and one of the respiratory studies were scrubbed. The cardiovascular study may have limited application since post-drug measurements were made only at 30 min (although C_{max} for zolpidem occurs at 1.8 hrs). Results in the other studies showed zolpidem to be minimally toxic.

Collignon/IIBE02 "Hemodynamic effects of oral zolpidem in patients with coronary insufficiency". This was an open-label study of the effects of single oral doses of zolpidem 10 mg administered during cardiac catheterization to patients (44-70 yrs of age) with coronary insufficiency. Hemodynamic parameters were measured 30 min post-drug. Eleven subjects entered study; results for 10 were evaluable. No clinically significant changes in haemodynamic parameters were seen. One CAD patient exhibited angina during coronary angiography 15 min after drug administration; another patient exhibited a brief period of confusion one hr post-drug. *[Vol 1.118/0001]*

Cirignotta/IIIT06 "Controlled polysomnographic study of the effects of benzodiazepine and non-benzodiazepine hypnotics in obstructive sleep apnea patients". This was a randomized double-blind study of single doses of zolpidem 20 mg vs flurazepam 30 mg and placebo using a balanced crossover design. Eligibility was limited to heavy snorers[a] with early obstructive apnea. Outcome measures included PSG variables, sleep questionnaires, and physician's global.

[a] The author's discussion of the pathophysiology of snoring, with an empirical system for grading severity, is reproduced at **Appendix I.**

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Nine of 12 (11 male, 1 female; age range, 38-64 yrs of age) subjects were normal subjects; 3 were insomniac; all had been referred because of the complaint of heavy snoring.
Patients spent one night in the sleep lab as an adaptation night; at least 6 days' washout occurred between study treatments.

Episodes of apnea were increased on both active treatments (198.2 ± 168.9, zolpidem; 145.1 ± 144.7 flurazepam; 104.1 ± 104.6 placebo). One patient complained of vertigo and fatigue in the morning after zolpidem, and two patients complained of dizziness, fatigue, and clumsiness in the morning after flurazepam. No other adverse effects were reported. *[Vol 1.114/0001]*

Lemercier/IIIFR17 "Study of the effects of zolpidem on respiratory parameters in patients with chronic respiratory failure". This was an open-label study of single oral doses of zolpidem 20 mg in patients with chronic respiratory failure (N=10, 56-75 yrs of age).

All subjects were taking theophylline; two were also receiving digoxin. Because baseline blood gas values were outside eligibility criteria for 8/10 patients, no conclusions could be drawn regarding the respiratory consequences of zolpidem treatment. It is of interest, however, that no adverse clinical events were reported. *[Vol 1.156/0001]*

Bercoff/IFR20 "Zolpidem and chronic hepatic insufficiency". This was an open-label study in which N=8 patients 31-65 yrs of age received single oral doses of zolpidem 20 mg in the morning. All 8 patients slept for approx 3 hrs. Plasma levels of zolpidem were increased 5x in comparison with those of middle-aged healthy volunteer controls (N=8): C_{max} = 499 vs 250 ng/ml, AUC = 4203 vs 788 ng/ml/hr. Elimination half-life was also increased ($t_{½}$ = 9.9 ± 2.9 hrs vs 2.2 ± 0.1 hrs). No adverse effects were observed. *[Vol 1.44/0002]*

Bouchet/IFR12 "Study of the pharmacokinetics of zolpidem in the patient with renal failure". This was an open-label study of zolpidem 10 mg administered by slow infusion in 24 patients 27-82 yrs of age with chronic renal failure (8, just prior to dialysis; 8, between dialysis session; 8, not undergoing dialysis). AUC, C_{max}, and $t_{½}$ were unchanged. No adverse reactions were seen in any subject. *[Vol 1,44.0059]*

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Lorizio/IIIT04 "Efficacy and safety of zolpidem vs flurazepam in depressed patients on imipramine: a double-blind, parallel group study". Duration of study was 10 days: 2 days placebo; 5 days active; 3 days placebo. Thirty patients with major depressive disorder were to be enrolled, but the study was discontinued after 11 patients had been empanelled. No clinically relevant adverse effects were recorded. *[Vol 1.170/0001]*

Pointel/IFR43 "Pharmacokinetics of zolpidem in obesity." This was an open-label study of two doses of zolpidem (8 mg IV and 10 mg p.o.) administered to N=20 otherwhile healthy obese (mean body weight 140% of ideal) subjects 19-38 yrs of age. Kinetic profile of zolpidem was unchanged. One subject vomited 15 min after the IV infusion. No other adverse effects were reported. *[Vol 1.44/0185]*

8.5.8 Drug-drug Interactions

In studies carried out during the initial development of zolpidem, interactions were observed between zolpidem and imipramine and between zolpidem and chlorpromazine. Studies designed to look for interactions found none between zolpidem and: alcohol or caffeine; haloperidol or other antidepressants; flumazenil (specific benzodiazepine antagonist); cimetidine or ranitidine; or digoxin or warfarin; and antipyrine.

Coupez/IBE04 "Interaction of zolpidem and alcohol in acute administration; comparison with triazolam." This was a randomized, double-blind crossover study in healthy male volunteers 21-30 yrs of age (N=12) of single oral doses of zolpidem 20 mg vs triazolam 0.5 mg and placebo given alone and 1 hr prior to the ingestion of 1.5 ml/kg body weight of 40% alcohol (vodka) mixed with orange juice. Self-ratings and psychomotor testing were carried out 1.5-2 hrs after study drug administration (ie, 30-60 min after consuming the alcohol). Blood levels of alcohol and test compounds were measured 2, 3, 4, and 6 hrs after dosing. Measures of subjective vigilance, memory and psychomotor performance were reduced by both test drugs. Alcohol alone did not affect test results, and there were no subjective or pharmacokinetic interactions between alcohol and either of the study compounds. Adverse effects (giddiness, transient diplopia, nausea, vomiting, and hiccups) occurred with equal frequency with both active treatments. *[Vol 1.45/0197]*

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Thebault/IFR06 "Determination of a possible pharmacodynamic interaction between zolpidem and alcohol." This was a double-blind crossover study in which N=12 healthy adult male volunteers 20-29 yrs of age received single doses of zolpidem 20 mg, flunitrazepam 2 mg, and placebo with and without alochol (red wine 6.5 ml/kg body weight). No pharmacokinetic or dynamic interaction between alcohol and study drug was observed; no adverse effects were reported. *[Vol 1.207/0001]*

Vandel/IFR26 "Study of a possible pharmacodynamic interaction between the oral administration of 300 mg of caffeine and 20 mg of zolpidem." This was a double-blind randomized crossover trial using a 4x4 Latin square design. Eight healthy volunteers (4 male, 4 female) 22-30 yrs of age participated. Outcome measures, in addition to pharmacokinetic parameters, were physician's ratings on the Stanford Sleeping Scale (q hr x 4 hrs, then q 2 hrs until awakening), a memory test, and subjective evaluations in the morning following treatment. Caffeine or blinded placebo was administered at 9:30 pm; zolpidem or placebo, 45 min later.

Zolpidem alone had a significant effect on the SSS 1 hr post-treatment; zolpidem + caffeine, at 2 hrs. Memory was not affected. Adverse effects seen with zolpidem were vertigo and diplopia; drowsiness on awakening occurred after all treatments. Insomnia was observed after caffeine alone. *[Vol 1.49/0046]*

Coupez/IBE02 "Study of the possible interaction between imipramine and zolpidem." This was an open trial using a 3x3 crossover design in which healthy male volunteers (N=6) 20-27 yrs of age received single doses of zolpidem 20 mg, imipramine 75 mg, or both compounds, at intervals of one week. Blood levels were measured at intervals; vigilance and well-being were self-rated at 3 hrs post-treatment. All subjects exhibited drowsiness after both study drugs; this was rated severe after the combination. 5/6 subjects also exhibited anterograde amnesia after the combination. *[Vol 1.45/0099]*

Harvengt/IBE03 "Study of possible pharmacodynamic and pharmacokinetic interaction between zolpidem and chlorpromazine." This was a double-blind crossover study of single doses of study drug vs placebo in six healthy volunteers (3 male, 3 female) 21-30 yrs of age. Concomitant administration of zolpidem 20 mg and chlorpromazine 50 mg resulted in impaired manual dexterity and conflict choice, as well as self-evalulation of vigilance, psychomotor performance, and self-control. Pharmacokinetic parameters of both drugs were unchanged. Adverse effects of zolpidem were sedation, diplopia, and slurred speech. *[Vol 1.47/0002]*

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Lambert/IFR21 "Zolpidem: Study of a potential clinical and pharmacokinetic interaction with haloperidol." This was a randomized double-blind trial of single doses of zolpidem 20 mg and haloperidol 2 mg in healthy male volunteers (N=6)21-26 yrs of age, using a 3x3 repeated measures Latin square design.

Adverse events (headaches, nausea, vomiting) were observed primarily during haloperidol administration; zolpidem was well tolerated. There was no pharmacokinetic interaction between study drugs; effects on vigilance were not potentiated. *[Vol 1.48/0002]*

Laxenaire/IIFR06 "Evaluation of zolpidem (15 and 30 mg) in a controlled trial vs triazolam (0.5 mg) in neurotic depressed patients." This was a randomized, double-blind balanced parallel-groups study of two doses of zolpidem vs triazolam 0.5 mg.

Study population consisted of N=36 hospitalized depressed patients (16 male, 20 female, mean age: 42 yrs). Twenty subjects were habitual users of hypnotics; 7/36 were described as frequent users; 26/36 patients were receiving antidepressants (clomipramine, haloperidol, levomepromazine, cyamemazine, sotalol).

One patient (a 72-yr old male hospitalized because of attempted suicide) was discontinued from zolpidem 30 mg on the 6th day because of confusion. Symptoms cleared after 12 hrs; clomipramine 75 mg/day was continued. Two other patients reported drug-related adverse effects at 30 mg: Patient 41-yr old female, had two episodes of orthostatic hypotension (90/50 mm Hg); Patient , 52-yr old female, had orthostatic hypotension (100/60 mm Hg) with tachycardia (HR=100). Both patients were receiving clomipramine 100 mg/day.

Patient a 26-yr old male, exhibited mood inversion (euphoria) as well as orthostatic hypotension (90/55 mm Hg) on days 5-11 of zolpidem 15 mg. Clomipramine was reduced from 75 to 50 mg/day and levomepromazine and heptaminol were added, with relief of symptoms. *[Vol 1.154/0001]*

Forster/ICH05 "Evaluation of the specific benzodiazepine antagonist flumazenil (Ro 15-1788) as an antagonist of zolpidem, a new non-benzodiazepine hypnotic imidazopyridine derivative." This was a randomized double-blind placebo-controlled study of single doses of study medication in healthy male volunteers (N=9) 18-40 yrs of age using a repeated measures crossover design. Study sessions were at least one wk apart; drugs were administered intravenously; zolpidem 0.21 mg/kg (or its placebo) always preceded flumazenil 0.04 mg/kg (or its placebo) by an interval of 17 min.

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The following outcome measures were used: EEG; psychomotor performance (track tracer); vital signs; ciliary reflex and response to verbal instructions (eye opening); anterograde and retrograde memory; and visual analog scale. Zolpidem blood levels were also obtained.

The report included in the NDA covers the first 6 subjects: mean HR increased from bpm at 2 min after zolpidem, and from bpm after zolpidem + flumazenil. There were 4 episodes of hiccups, 3 following zolpidem alone, and one following zolpidem + flumazenil. No pharmacokinetic interaction was observed. *[Vol 1.46/0002]*

Harvengt/IBE05 "Study of possible pharmacodynamic and/or pharmacokinetic interactions between zolpidem and the histamine H_2 receptor antagonists cimetidine and ranitidine." This was an open-label study of single doses of zolpidem 20 mg alone and on days 1 and 19 of the two anti-H_2 treatments in healthy volunteers (3 male, 3 female) 21-27 yrs of age. Cimetidine 200 mg was given tid with meals and 400 mg at hs; ranitidine was given 150 mg bid.

No pharmacokinetic interactions were observed. Nausea and headache were seen after antihistamine treatment; sedation and diplopia were seen after every dose of zolpidem; two subjects had hiccups; three subjects did not remember the tests taken after zolpidem administration. *[Vol 1.47/0150]*

Meyer/IFR39 "Screening for a pharmacological interaction between zolpidem and digoxin." This was an open-label trial of repeated doses of zolpidem 10 mg and digoxin 0.25 mg in healthy male volunteers (N=10) 21-33 yrs of age. Digoxin was administered daily x 7 days to obtain steady-state plasma levels. After a one-day drug holiday, subjects received digoxin (8 am) and zolpidem (11 pm) x 7 days. Mean peak concentrations and mean AUC of digoxin did not differ between the two periods, and no clinical signs of digitalis intoxication were observed. Headache, diarrhea, fatigue, and tachycardia were observed after digoxin; vomiting was seen once 45 min after the administration of zolpidem. *[Vol 1.48/0081]*

Warrington/IGB05 "Study of the possible modification of the anticoagulant action of warfarin by zolpidem after repeated administration to healthy volunteers." This was an open label study in healthy male volunteers (N=8) 20-30 yrs of age. Subjects received a daily dose of warfarin (x 10 days) sufficient to prolong their prothrombin time to 1.5x base value. Zolpidem 20 mg hs was then added to treatment x 4 nights. Subsquent warfarin values were unchanged. There were no drug-related TEAEs. *[Vol 1.213/0001]*

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Albin/IFR24 "Study of zolpidem kinetics undertaken in man during repeated treatment; effect on antipyrine clearance test." This was an open study in healthy male volunteers (N=12) 21-36 yrs of age, using a dose of zolpidem of 20 mg x 15 nights. Antipyrine was given in a dose of 1.0 gram on the day prior to, and the day following, zolpidem treatment. Zolpidem kinetics were determined during the night following the first and last doses. No change in zolpidem kinetics was observed after single or repeated doses; no accumulation was observed. The kinetic profile of antipyrine was unaffected. *[Vol 1.45/0002]*

8.5.9 Withdrawal Phenomena, Abuse Potential

a) The sponsor conducted 4 studies of the abuse potential of zolpidem. Results are currently under review by Drug Abuse staff (HFD-007). Clinically, there is little of concern in these studies: adverse effects at lower doses were manageable, and may in fact have been related to the subjects' prior history of substance abuse.

LSH13 This was a single-blind pilot dose-escalation study by Jasinski to select appropriate doses for a study of the drug's abuse potential. Design was a Latin square; diazepam and placebo were used as controls. Subjects (N=4) were healthy male volunteers with a history of drug abuse who were neither requiring nor requesting treatment for their substance abuse; all subjects completed study. A maximum dose of zolpidem of 90 mg was permitted, although marked sedation in all subjects limited the dose to 40.

Four subjects entered and completed the study. Subjective profile of effects was considered benzodiazepine-like. Compared with diazepam, the effects of zolpidem were shorter-lasting; on a milligram basis, zolpidem was judged half as potent as diazepam with respect to abuse potential.

Adverse effects other than sedation were: Subject - pre-/post-study increase in AST from 95 to 169 IU/L (normal range: 0-30); Subject - confusion, auras, diplopia, and blurred vision after zolpidem 40 mg; Subject - blurred vision on diazepam 20 mg; rhinorrhea, singultus, disinhibition and hallucinations after zolpidem 10 mg. *[Vol 1.92/0001]*

LSH14 This was a randomized, double-blind, crossover study by Jasinski of the abuse potential of single doses of zolpidem 10, 20, and 40 mg vs diazepam 10 mg.

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Outcome measures were subject and observer questionnaires. N=14 healthy male volunteers with a history of substance abuse (but not requesting or requiring treatment for their bstance abuse at the time of this study, and with a negative ur scr.een at entry) were randomized; 12 subjects completed all trea s. The profile of subjective effects of zolpidem was similar t of diazepam. Zolpidem produced less sedation but an increa. the "drunk, "confused" and "do distances, colors and shapes appear changed" scales, compared with diazepam. One subject discontinued because of a TEAE. See **8.3 Significant Events Considered Possibly, Probably, or Definitely Drug-Related.** *[Vol 1.93/0001]*

LSH15 This was a single-blind pilot dose-escalation study by Griffiths in healthy male outpatient volunteers who were substance abusers, age 18-50, not requesting or requiring treatment for their addiction. Zolpidem was presented in increasing doses from 5 to 80 mg, each dose alternating with placebo; triazolam 0.5 mg was administered as the last active treatment. Subject-rated measures of effect were the primary efficacy variables; safety monitoring included pre- and post-treatment physical/lab exams and reports of adverse effects. Vital signs were monitored throughout each study session.

Ten subjects qualified for study: 2/5 subjects completed, the others discontinuing at lower doses because of limiting sedative effect. For subjects completing study, triazolam 0.5 mg was most comparable to zolpidem 20 and 40 mg.

Only two subjects experienced adverse effects: Subject vomited x4 after receiving zolpidem 40 mg; Subject experienced confusion and delusions after zolpidem 60 mg. *[Amendment 2/12/90]*

LSH16 This was a double-blind randomized placebo- and triazolam-controlled crossover study by Griffiths in outpatient male volunteers with histories of sedative drug abuse who were otherwise in good health. Pre-study evaluations included history and physical examination, including vital signs; ECG; clinical lab studies; urine drug screen; and medical history. Study design called for nine daily sessions, without washout, each session lasting from 9 am to 5 pm. Doses used were zolpidem 15, 30, and 45 mg; triazolam 0.25, 0.5, and 0.75 mg, and placebo. Rating scales, psychomotor performance tests, balance and reaction time tests, vital signs, and observer ratings were the end-points.

N=18 subjects were randomized; 15 completed study; 3 subjects were d/c after one study session because of positive urine screens.

- cont'd -

Both zolpidem and triazolam produced dose- and time-related impairment on subjective and behavioral measures. Onset was rapid (0.5-1 hr), with no difference between actives. Zolpidem was rated 50x less potent than triazolam on parameters relating to drug liking. Performance returned to normal by the end of each day's session. Five subjects vomited after the highest dose of zolpidem; 4 subjects, after lower doses. There were no other adverse effects. *[Amendment 2/12/90]*

b) There was no evidence for the development of tolerance in either of the two Lorex trials in chronic insomniacs. In LSH the 31-night outpatient study, sSL and sTST remained at or near Week 2 values throughout treatment.

In LSH the 35-night sleep lab study, overall comparison among treatment groups of change from first to fifth week on active drug showed no loss of efficacy. These findings provide some assurance that dose-escalation will not be a problem.

8.5.10 Human Reproduction Data

There are no studies in pregnant women. Reproduction studies in rats and rabbits at doses up to 875x the human dose have shown no evidence of impaired fertility or harm to the fetus. Draft labelling places zolpidem in Pregnancy Category B.

In a study in lactating mothers (Olive/IFR31, N=5) the half-life of zolpidem was similar to that in young normal volunteers (2.6 ± 0.3 hrs). Between 0.004 and 0.011% of the administered dose was excreted in breast milk; the effect on the nursling was not evaluated. *[Vol 1.40/0002]*

8.5.11 Premedicant Studies *[Vol 1.54/0150 and 5/23/91 Amendment]*

The safety and efficacy of zolpidem as a premedicant in adult patients was investigated by LERS in 12 single-center studies in three countries (France, Switzerland, UK). These were single dose studies in which subjects received oral zolpidem, placebo, or a benzodiazepine control approx 1 hr before elective surgery. The distribution of subjects was as follows:

- cont'd -

	Zolpidem	Active[a]	Placebo	Total
Controlled (8)	394	329	167	890
Open (4)	210	-	-	210
Totals	604	329	167	1,100

[a] Diazepam 10 mg, flunitrazepam 1 & 2 mg. lorazepam 1, 2, 2.5 mg, midazolam 7.5 & 15 mg.

Zolpidem doses of 5-30 mg were employed. In 2/8 controlled studies (**Duvaldestin/IIFR14** and **Gemperle/IICH01**), subjects received a dose of study medication at bedtime the night before surgery. Distribution of zolpidem subjects, by dose and type of study, is shown below.

	5 mg	10 mg	15 mg	20 mg	30 mg	Total
Controlled	-	134	-	244	16	394
Open	26	57	51	59	17	210
Totals	26	191	51	303	33	604

Seven adverse events occurred with a frequency ≥1% among the 378 patients randomized to 10 or 20 mg zolpidem, as follows:

	Zolpidem	Active	Placebo
N	378	167	329
Dizziness/vertigo	36 (10%)	23 (7%)	4 (2%)
Headache	22 (6%)	23 (7%)	12 (7%)
Nausea/vomiting	20 (5%)	6 (2%)	6 (4%)
Visual disturbance	17 (4%)	3 (1%)	0
Agitation	13 (3%)	4 (1%)	4 (2%)
Fatigue	5 (1%)	7 (2%)	0
Emotional instability	4 (1%)	4 (1%)	0

Three episodes of tachycardia (one each on zolpidem, lorazepam, and midazolam) were noted in the seven studies in which general or regional anesthesia was used. No other severe, unusual or unexpected adverse effects were encountered.

9.0 Labelling Review

A brief review of sponsor's draft labelling (5.17.91) follows:

- cont'd -

Pharmacodynamics

Labelling makes claims with respect to sleep latency, total sleep time, perceived number of awakenings, and sleep architecture, based on sleep laboratory studies in noninsomniac adults, including those over 60 years of age. The following table summarizes these data from the four principal efficacy trials in adults and the dose-ranging trial in elderly subjects (numerator = statistically significant differences from placebo; denominator = outcome measures for doses ≤10 mg):

	LSH 35-night	LSH 31-night	LSH 1-night	LSH 1-night	LSH11 2-night	Totals
dec SL	4/5	-	2/2	0/2	2/2	8/11
inc SE/TST	4/5	-	2/2	1/2	2/2	9/11
inc Stage 3/4	0/5	-	1/2	0/2	0/2	1/11
%REM unchanged	2/2	-	0/2	1/2	1/2	4/8
dec sSL	2/5	4/4	2/2	0/2	2/2	10/15
inc sTST	1/5	1/4	0/2	1/2	2/2	5/15
dec sNA	0/5	1/4	2/2	0/2	2/2	5/15
SQ improved	0/5	1/4	2/2	1/2	2/2	6/15

The data show that at doses ≤10 mg zolpidem consistently decreased the time to fall asleep and increased total sleep time. Stage 3/4 was unchanged; REM sleep was preserved at recommended doses at 4/8 time points, and showed a statistically significant decrease at the other 4/8 points.

These effects were accompanied by subjective perceptions of reduced time to fall asleep, but not by an increase in subjective perception of sleep duration or sleep quality.

Sponsor's labelling in regard to residual effects are supported by the data.

Amnesia, usually manifested as single events of morning forgetfulness, was dose- and age-related.

Indications

A maximum dose of 10 mg is recommended, with elderly and debilitated patients to be started on 5 mg. The present reviewer concurs in these recommendations.

- cont'd -

Labelling states that PSG data support the claim that zolpidem decreases number of awakenings (NA) and improves sleep quality (SQ). In the summary table above, sNA was positive on only 5/15 measures; SQ, on 6/15.

Warnings

Labelling states that the combined effects of zolpidem 20 mg and the equivalent of 3 oz. of ethanol have not been shown to be greater than the effects of zolpidem alone. Labelling should note the limitations of these data, as discussed below.

Precautions

Labelling with respect to overdose, respiratory suppression, and use in patients with impaired renal/hepatic function appears reasonable.

Drug Interactions

Labelling states that "the combined effects of zolpidem 20 mg and 3 oz of alcohol have not been shown to be greater than the efects of zolpidem alone." More accurately, the combined effects "have been shown not to be greater" than those of zolpidem alone. It should be noted that in the study in which these data were collected (**Coupez/IBE04**) subjects were given study drug 1 hr before being given alcohol; the sequence of alcohol followed by study drug was not tested, nor was simultaneous administration.

Adverse Reactions

As discussed in this review, sponsor's 1% table combines data from all six efficacy studies. A 1% table based on **LSH** is proposed. Only four TEAEs not reported in that study occurred in controlled studies with a frequency ≥0.5%:

	Zolpidem N=576	Placebo N=26
dry mouth	5 (0.9%)	1 (0.4%)
urinary tract infection	4 (0.7%)	1 (0.4%)
allergy	3 (0.5%)	0
taste perversion	3 (0.5%)	0

- cont'd -

10.0 Conclusions

The adequate and well-controlled studies carried out by the US sponsor, two in insomnia and two in insomnia, provide substantial evidence that zolpidem will have the effect it is represented to have under the conditions of use suggested in proposed labeling. Treatment under controlled conditions has been carried out for at least 30 days with no loss of efficacy or development of tolerance. Rebound, looked for in all efficacy trials, was not observed.

The safety data base of 3,400 subjects, and the analyses presented by the sponsor, are adequate for assessing the safety of zolpidem in clinical practice. The pattern of adverse effects is similar to that of benzodiazepine sedative-hypnotics. No serious or unexpected adverse effects were reported; no adverse effects on laboratory parameters were observed. Amnesia was age- and dose-related; events were of minor clinical concern. Evidence of impaired psychomotor function was minimal.

Use of zolpidem in the elderly -- extensively studied in the European development program -- was not marked by unusual, more frequent, or more severe adverse effects. The 4 subjects who experienced falls were ≥60 yrs of age; 3/4 were receiving zolpidem 20 mg.

11.0 Recommendations

1. Approve.
2. Starting dose 10 mg (5 mg for elderly and disabled), as proposed.
3. Use of zolpidem as a premedicant is contraindicated.

David M Collins, MD

cc: NDA
HFD-120
HFD-120/Laughren
/Mille
/Collins
HFD-713/RSrinivasan
ft/dmc/07/08/91

Appendix A

Reference: 6.0 Description of Clinical Data Sources

List of investigators

Name	City, State/Country	Studies
LERS		
Albin, H	Bordeaux, France	IFR24
Apoil, A	Paris, France	IIFR09
Bercoff, E	Bois Guillaume, France	IFR20
Blatrix, C	Creteil, France	IFR13
Borbely, A A	Zurich, Switzerland	ICH03
Bouchet, J L	Bordeaux, France	IFR12
Cirignotta, F	Bologna, Italy	IIITO6
Colle, H	Bordeaux, France	IFR42
Collignon,	Liege, Belgium	IIBE02
Coupez, JM	Brussels, Belgium	IBE01
		IBE02
		IBE04
		IIBE01
Court, I	Creteil, France	IFR05
Doyard, P	Hyeres, France	IIFR15
Dupuy, B	Cherbourg, France	IIIFR07
Emeriau, JP	Pessac, France	IFR25
		IIFR05
		IIIFR10
Ferreri, M	Paris, France	IIIFR01
Feuerstein, Cl	Grenoble, France	IFR04
Forette, B	Paris, France	IFR34
Forster, A	Geneva, Switzerland	ICH05
Gaillard, J M	Geneva, Switzerland	ICH01
Grilliat, J P	Nancy, France	IFR22
Hamdy, R C	London, England	IIGB08
Harvengt, C	Brussels, Belgium	IBE03
		IBE05
Herrmann, W M	Berlin, FRG	IIGE06
Kummer, J	Nordschwarzwald, FRG	IIGE02/03
Kunstler, M	Brussels, Belgium	IIIBE01
Kurtz, D	Strasbourg, France	IFR38
Lambert, B	Dijon, France	IFR08
		IFR21
Laxenaire, M	Dommartin-Les-Toul,France	IIFR06
Lemercier, J P	Rouen, France	IIFR17
Liebau, H	Lienfelden-Echterdingen, FRG	IIIGE02
Linden, J	Nordschwarzwald, FRG	IIIGE01

- cont'd -

Appendix A - cont'd

Name	City, State/Country	Studies
Lorizio, A	Parma, Italy	IIIT01/02
		IIIT04
Maarek, L	Soissons, France	IIFR10
		IIIT04
Maggioni, M	Milan, Italy	IIIT03
Maillard, D	Paris, France	IFR27
Meyer, P	Paris, France	IFR39
Monti, J M	Montevideo, Uruguay	IIUR01
Nicholson, A N	Farnborough, England	IGB02/08
Olive, G	Paris, France	IFR31
Oswald, I	Edinburgh, Scotland	IIGB01
Pacifici, G M	Pisa, Italy	IIT01
Pagot, R	Vannes, France	IIIFR04
Perret, J E	Grenoble, France	IIFR01
Pointel, J P	Dammartin-Les-Toul, France	IFR43
Ribeyre, J P	Poritault Combault, France	IIFR11
Richens, A	Cardiff, Wales	IGB03
Rizzo, P A	Rome, Italy	IIIT05
Roger, M	Villiers le Bel, France	IFR10
		IIIFR08
		IIIFR18
Rulliere, R	Paris, France	IFR01
Ruther, E	Munich, FRG	IGE01
Shaw, S H	Wakefield W, England	IIGB10
Simon, P	Paris, France	IFR29/35
Terzano, M G	Parma, Italy	IIT02
Thebault, J J	Creteil, France	IFR02
		IFR03
		IFR06
		IFR09
		IFR11
		IFR17
		IFR23
		IFR30
Torhorst, A	Munich, FRG	IIGE01
Valla, A	Caen, France	IIFR02
Vandel, B	Besancon, France	IFR26
		IIR28
Warrington, S J	London, England	IGB01
		IGB05
		IGB09
Wheatley, D	Twickenham, England	IIIGB01

- cont'd -

Appendix A - cont'd

Name	City, State/Country	Studies
Lorex		
Cohn, J B	Long Beach, CA	LSH
Cohn, M A	Miami Beach, FL	LSH04
		LSH07
Docherty, J P	Nashua, NH	LSH
Fillingim, JM	Savannah, GA	LSH
Griffiths, R R	Baltimore, MD	LSH15
		LSH16
Jasinski, D	Baltimore, MD	LSH13
		LSH14
Kann, J	Pittsburgh, PA	LSH
Lahmeyer, H W	Chicago, IL	LSH
Leese, P T	Kansas City, MO	LSH05
		LSH06
Leppik, I E	Minneapolis, MN	LSH
Mendels, J	Philadelphia, PA	LSH12
Roth, T	Detroit, MI	LSH02
		LSH
		LSH
Scharf, M B	Cincinnati, OH	LSH03
		LSH11
		LSH12
		LSH
		LSH12
		LSH
Thorpy, M	Bronx, NY	LSH12
Vogel, G W	Atlanta, GA	LSH
		LSH
Walsh, J K	St Louis, Mo	LSH
		LSH
Weintraub, M	Rochester, NY	LSH01
Weiss, B	Miami Beach, FL	LSH12

Appendix B

Reference: **6.1.1 Study Type and Design**

Routine safety data from the following studies (22 controlled, 8 uncontrolled) are included in the Integrated Safety Summary. With the exception of **Coupez/IIBE01**, a study of zolpidem kinetics, they are efficacy and safety trials of zolpidem as an hypnotic. **Doyard/IIFR15**, an open-label study, was carried out in children 3.5-24 yrs of age. *[Synopses, Vol 1.53]*

	Zolpidem	Active	Placebo	X-O	Total
Controlled:					
* **Apoil/IIFR09**	52	52[a]	-	52	52
Blatrix/IFR13	28	-	28	28	28
* **Coupez/IIBE01**	15	16[b]	-	-	31
Dupuy/IIIFR07	64	29[c]	-	-	93
* **Emeriau/IIIFR10**	52	28[c]	-	-	80
* **Ferreri/IIIFR01**	132	128[a]	-	-	260
* **Hamdy/IIGB08**	06	-	03	-	09
* **Kunstler/IIIBE01**	31	29[c]	-	-	60
Laxenaire/IIFR06	24	12[a]	-	-	36
* **Lorizio/IIITO1**	60	-	-	-	60
* **Lorizio/IIITO4**	06	05[d]	-	-	11
* **Maarek/IIFR10**	40	40[a]	-	40	40
* **Maggioni/IIITO3**	21	19[c]	-	-	40
* **Pagot/IIIFR04**	47	48[a]	-	-	95
Perret/IIFR01	28	-	28	28	28
* **Ribeyre/IIFR11**	22	21[e]	-	21	22
Roger/IFR10	88	-	23	-	111
Roger/IIIFR18	141	77[a]	-	-	218
* **Shaw/IIGB10**	80	-	39	-	119
* **Torhorst/IIGE01**	02	02[f]	-	02	02
* **Valla/IIFR02**	24	-	-	-	24
* **Wheatley/IIIGB01**	54	-	33	-	87
Totals	1,017	506	154	171	1,506

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* Clinical lab data available.
a = triazolam; b = flunitrazepam; c = oxazepam;
d = flurazepam; e = nitrazepam; f = chloral hydrate.

- cont'd -

Appendix B - cont'd

	Zolpidem	Active	Placebo	X-O	Total
Uncontrolled:					
* Doyard/IIFR15	20	-	-	-	20
Emeriau/IIFR05	20	-	-	-	20
* Kummer/IIGE02/03	10	-	-	-	10
* Liebau/IIIGE902	107	-	-	-	107
Linden/IIIGE01	16	-	-	-	16
* Maarek/IIIFR11	96	-	-	-	96
Monti/IIUR01	06	-	-	-	06
* Roger/IIIFR08	44	-	-	-	44
Totals	319	-	-	-	319
TOTALS	1,336	506	154	171	1,825

Appendix C

Reference: **6.1.1 Study Type and Design**

The following controlled studies of zolpidem as an hypnotic that were carried out by are included in the Integrated Safety Summary with respect to deaths and dropouts, but not with respect to routine safety data (labs, vital signs, etc):

Study	M	F	Age range	Location of report
Pharmacokinetics:				
Colle/IFR42	12	-	23-36 yrs	*Vol 1.116*
Feuerstein/IFR04	02	02	24-26 "	" *1.138*
Grilliat/IFR22	04	05	23-33 "	" *1.142*
*** **Harvengt/IBE03**	03	03	21-23 "	" *1.144*
*** **Lambert/IFR21**	06	-	21-26 "	" *1.153*
Simon/IFR29/35	12	-	18-28 "	" *1.202*
*** **Thebault/IFR06**	12	-	20-29 "	" *1.207*
*** **Vandel/IFR26**	04	04	22-30 "	" *1.211*
	55	14		
Pharmacodynamics:				
** **Cirignotta/IIITO6**	11	01	38-64 "	" *1.114-5*
* **Colle/IFR44**	10	02	6-14 "	" *1.117*
*** **Coupez/IBE04**	12	-	21-30 "	" *1.121*
*** **Forster/ICH05**	09	-	18-40 "	" *1.140*
Maillard/IFR27	08	08	21-33 "	" *1.177*
Nicholson/IGB02/08	18	-	18-52 "	" *1.180*
Richens/IGB03	12	-	20-30 "	" *1.189*
Rizzo/IIIT05	04	08	19-41 "	" *1.190*
Terzano/IIT02	06	06	19-29 "	" *1.203-4*
Thebault/IFR23	06	-	23-38 "	" *1.208*
	96	25		
Phase II/III:				
Borbely/ICH03	05	04	24-46 "	" *1.112*
Gaillard/ICH01	05	06	20-28 "	" *1.141*
Oswald/IIGB01	03	09	47-69 "	" *1.181*
Ruther/IGE01	10	-	23-36 "	" *1.199*
	23	19		
Totals	174	58		
Total (22)	232	(Avg N=11/study; range: 04-18)		

* See **8.5.6 Drug-Demographic Interactions.**
** See **8.5.7 Drug-Disease Interactions.**
*** See **8.5.8 Drug-Drug Interactions.**

- cont'd -

Appendix C - cont'd

The fcllowing open/SB hypnotic studies by are included in the Integrated Safety Summary with respect to deaths and dropouts, but not with respect to routine safety data (labs, vital signs, etc). Brief summaries of studies identified with one or more asterisks are included in this review as indicated.

Study	M	F	Age range	Location of report
Pharmacokinetics:				
*** **Albin/IFR24**	12	-	21-36 yrs	*Vol 1.45*
Coupez/IBE01	16	-	19-39 "	" *1.119*
*** **Coupez/IBE02**	06	-	20-27 "	" *1.120*
*** **Harvengt/IBE05**	03	03	21-27 "	" *1.145*
Olive/IFR31	-	05	27-36 "	" *1.40*
Thebault/IFR09	09	-	22-31 "	" *1.43*
Thebault/IFR17/30	04	04	25-40 "	" *1.41*
* **Vandel/IFR28**	20	19	19-45 "	" *1.212*
Warrington/IGB01	03	-	19-23 "	" *1.41*
Warrington/IGB09	10	10	21-36 "	" *1.41*
	83	41		
Pharmacodynamics:				
** **Bercoff/IFR20**	14	02	31-65 "	" *1.110*
** **Bouchet/IFR12**	16	08	27-82 "	" *1.113*
** **Collignon/IIBE02**	07	04	44-70 "	" *1.118*
Court/IFR05	04	-	22-27 "	" *1.124*
* **Emeriau/IFR25**	03	05	70-85 "	" *1.128*
* **Forette/IFR34**	12	07	19-31/81-95 yrs	" *1.139*[a]
* **Kurtz/IFR38**	05	07	60-74 yrs	" *1.152*
* **Lambert/IFR08**	04	02	70-84 "	" *1.42*
** **Lemercier/IIIFR17**	05	05	56-75 "	" *1.156*
*** **Meyer/IFR39**	10	-	21-33 "	" *1.178*
** **Pointel/IFR43**	10	10	19-38 "	" *1.186*
* **Thebault/IFR11**	08	-	46-59 "	" *1.42*
Thebault/IFR03	03	-	22-39 "	" *1.206*
*** **Warrington/IGB05**	08	-	20-36 "	" *1.213*
	109	50		

* See **8.5.6** **Drug-Demographic Interactions.**
** See **8.5.7** **Drug-Disease Interactions.**
*** See **8.5.8** **Drug-Drug Interactions.**

[a] The 81-95 yr olds (2 male, 7 female) were the subjects; the younger males (N=10) served as controls.

- cont'd -

Appendix C - cont'd

Study	M	F	Age range	Location of report
Phase I/II/III:				
Herrmann/IIGE06	04	06	36-65 yrs	*Vol 1.146*
Roger/IIIFR08	07	37	49-100 "	" *1.192*
Rulliere/IFR01	06	03	22-40 "	" *1.198*
Thebault/IFR02	09	-	21-37 "	" *1.205*
	26	46		
Totals	218	137		

TOTAL (29 studies) = 355 (Avg N=13/study; range:

GRAND TOTAL (51 studies) = 232 + 355 = 587 subjects

- cont'd -

DESCRIPTION AND POPULATION OF THE 12 PREMEDICANT STUDIES IN ADULTS

A-Studies Vs. Placebo

Study	Total Cases	Sex M	F	Age Min Max	Zolpidem 5 mg	10 mg	15 mg	20 mg	30 mg	Placebo	BDZ*
Jones/ IIGB04	37		37	20-63		12		12		13	
Wilkinson/ IIGB14	53	37	16	18-60				18		18	17 (DZP 10mg)
Salem/ IIGB15	90	79	11	20-71				30		30	30 (DZP 10mg)
Paymaster/ IIGB13	90	45	45	17-69				30		30	30 (LRZ 2mg)
Gemperle/** IICH01	91	62	29	16-69				31		30	30 (MDZ 15mg)
Duvaldestin/** IIFR14	247	112	135	17-64		50		51		46	47 (LRZ 1mg) 53 (LRZ 2.5mg)
SUBTOTAL	608	335	273	16-71		62		172		167	207
B-Studies Vs. Benzodiazepines alone.											
Valla/ Verwaerde/IIFR13	60	40	20	23-75		20		20			20 (DZP 10mg)
Audebert/ IIIFR17	222	1	221	17-74		52		52	16		51 (FNZ 1mg) 51 (FNZ 2mg)
SUBTOTAL Studies Vs. Benzodiazapines alone.	282	41	241	17-75		72		72	16		122 (FNZ 2mg)
SUBTOTAL Controlled Studies	890	376	514	16-75		134		244	16	167	329
C-Uncontrolled Studies											
Jones/ IIGB03	40		40	18-62	10	10	10	10			
Wilkinson/ IIGB09	20	7	13	27-60		[illegible]		7	7		
Paymaster/ IIGB07	75		75	16-77	16	16	16	17	10		
Paymaster/ Salem/IIGB11	75	20	55	17-70		25	25	25			
SUBTOTAL Uncontrolled studies	210	27	183	16-77	26	57	51	59	17		
Overall	1100	403	697	16-77	26	191	51	303	33	167	329

* DZP: diazepam; LRZ: lorazepam; MDZ: midazolam; FNZ: flunitrazepam

** Zolpidem, placebo, benzodiazepines also administered the evening before surgery

Appendix D

Reference: **6.1.1 Study Type and Design**

Attached is sponsor's Table II.A.1 listing studies carried out under IND

TABLE II.A.1

Listing of Lorex Studies Presented in the Integrated Safety Summary

Type of Study/ Study Number	N	Treatment Objective	Doses	Duration
Clinical Pharmacology				
LSH03	15	Dose Tolerance	20-90 mg	Single dose, rising dose over 8 weeks
LSH04	12	Respiratory Effects	10-20 mg Codeine Placebo	Single doses, 4-period crossover
LSH05	10	Respiratory Effects	40 mg Codeine	Open, two-period, single doses
LSH06	90	Respiratory Effects	20 mg Codeine Placebo	Single dose
LSH07	14	Respiratory Effects	10-40 mg Codeine	Open, two-period single doses
LSH13	4	Abuse Potential In-patient	5-40 mg Diazepam Placebo	Single dose per treatment
LSH14	14	Abuse Potential In-patient	10, 20, 40 mg Diazepam Placebo	Single dose per treatment
LSH15*	9	Abuse Potential Outpatient	5-80 mg Triazolam Placebo	Single dose per active treatment alternated with placebo treatment
LSH16*	18	Abuse Potential Outpatient	15, 30, 45 mg Triazolam Placebo	Single dose per treatment
Controlled Efficacy				
LSH02	12	Dose Response	2.5-20 mg	Two consecutive doses per period in a 6-period crossover
LSH11	35	Elderly Subjects	A:plc/10/20 mg B:plc/5/15 mg	3-period crossover two consecutive doses per period
Uncontrolled				
LSH01	13	Dose Preference	10-40 mg	Single doses, two consecutive nights
LSH12	229	Long-Term Safety	15 mg (10 mg)	12 weeks

* Final study reports were not available at the time of submission

Appendix E

Reference: 6.1.2 Demographics

Sponsor's tables summarizing demographic characteristics of the study population are attached Table III.A.4; Lorex, Table II.A.3). *[Vol 1.54/0099 and 0047, respectively]*

The studies focused on the evaluation of zolpidem in a population considerably older than that evaluated by Lorex, with 755 of the 1320 (57%) study participants aged 60 or older. In the trials, the mean age was 61 years, as compared to a mean of 3.. in the Lorex studies. trials also included approximately twice as many females as males (Table III.A.4). Race was not collected in the majority of the studies.

TABLE III.A.4

Demographic Characteristics of Study Participants Exposed to Zolpidem

	Study Type		
	Controlled	Uncontrolled	Overall
N*	1014	306	1320
Age (yrs)			
N	1011	306	1317
Mean	60.2	63.7	61.0
S.D.	19.7	16.6	18.9
Min	18.0	16.0	16.0
Max	99.0	100	100
Gender			
N	1013	306	1319
Male	346	88	434
Female	667	218	885
Weight (kg)			
N	900	305	1205
Mean	61.9	66.4	63.0
S.D.	13.5	14.0	13.9
Min	25.9	33.0	25.9
Max	116.0	120.0	120.0
Other	0	0	0

*N under each variable shows the number of patients with available data for that variable

The demographic characteristics presented in Table II.A.3 show that the clinical pharmacology studies focused on the evaluation of zolpidem in healthy, young male volunteers (mean age = 28.0). The controlled efficacy trials examined a slightly older population (35.1 years) of both subjects (n = 543) and patients (n = 215) that included females (33.1%). Mean age was the highest (41.8 years) in the uncontrolled studies of patients with sleep disturbances. In these studies, the ratio of males to females was approximately 1:1.

TABLE II.A.3

Demographic Characteristics, by Study Type

	Clinical Pharmacology	Controlled	Uncontrolled	Overall
# Patients	186	758	242	1186
Age (yrs)				
Mean	28.0	35.1	41.8	35.3
S.D.	5.5	13.6	11.6	12.9
Min	18.0	18.0	19.0	18.0
Max	45.0	76.0	67.0	78.0
Gender				
Male	186	507	119	812
Female	0	251	123	374
Weight (kg)				
Mean	75.4	75.5	73.5	75.1
S.D.	12.7	14.4	16.2	14.5
Min	51.1	42.3	46.0	42.3
Max	117.7	138.6	160.0	160.0
Race				
White	110	642	198	950
Black	70	92	41	203
Other	6	24	3	33

Appendix F

Reference: **6.1.3 Extent of Exposure**

Sponsor's tables of dose and duration of exposure to zolpidem in LERS (Table III.A.8, hypnotics) and Lorex (Table II.A.9) studies are attached. Note that data are given for mean doses; Lorex data are for actual doses.

Dose levels in the single-dose premedicant studies are shown in **Appendix C.**

A range of doses was tested in the short-term (≤ 2 days), medium-term (3-28 days), and long-term (≥ 1 month) studies (Table III.A.8). In each of these duration categories, 10 and 20 mg were the most commonly tested doses.

TABLE III.A.8.

Duration of Exposure to Zolpidem in Studies by Actual Mean Dose

Study Type	Zolpidem Dose (mg)	1-2 Nights	3-7 Nights	8-28 Nights	≥ 1 Month
Controlled	2.5	0	0	1	0
	5	22	0	67	0
	10	31	65	187	1
	15	0	12	3	1
	20	44	147	221	166
	30	24	11	2	6
	>35	0	0	0	3
	Total	121	235	481	177
Uncontrolled	5	0	1	1	1
	7.5	0	2	7	0
	10	7	5	16	70
	15	0	0	6	30
	20	3	0	22	120
	30	0	0	0	11
	>30	0	0	0	4
	Total	10	8	52	236
Overall	2.5	0	0	1	0
	5	22	1	68	1
	7.5	0	2	7	0
	10	38	70	203	71
	15	0	12	9	31
	20	47	147	243	286
	30	24	11	2	17
	>35	0	0	0	7
	Total	131	243	533	413

Of the doses tested, 15 mg was evaluated most often (Table II.A.9) and was administered for the longest duration in all studies.

TABLE II.A.9

Actual Duration of Patient Exposure to Treatment, by Dose (All Studies)

Dose (mg)	1-2 Days	3-7 Days	1-2 Weeks	3-6 Weeks	> 6 Weeks
PLC	216	55	1	71	0
2.5	12				
5	110				
7.5	114				
10	195	4	5	70	18
15	105	25	21	100	147
20	185				
30	32				
40	52				
45	16				
50	9				
60	13				
70	9				
80	7				
90	4				

Appendix G

Reference: **8.5.1 ADR Incidence Tables**

Following is a list of TEAEs reported in Lorex controlled trials with greater frequency by placebo patients than by those on zolpidem.

	Zolpidem N=576	Placebo N=256
arthralgia	3 (0.5%)	4 (1.6%)
back pain	3 (0.5%)	3 (1.2%)
rhinitis	3 (0.5%)	3 (1.2%)
insomnia	2 (0.3%)	2 (0.8%)
abdominal pain	2 (0.3%)	2 (0.8%)
tooth disorder	2 (0.3%)	1 (0.4%)
depression	2 (0.3%)	1 (0.4%)
dysmenorrhea	2 (0.3%)	1 (0.4%)
fever	1 (0.2%)	3 (1.2%)
arthritis	1 (0.2%)	1 (0.4%)
coughing	1 (0.2%)	1 (0.4%)
abdomen enlarged	0	1 (0.4%)
hypertension	0	1 (0.4%)
hyperaesthesia	0	1 (0.4%)
migraine	0	1 (0.4%)
paresthesia	0	1 (0.4%)
gastroenteritis	0	1 (0.4%)
tachycardia	0	1 (0.4%)
nervousness	0	1 (0.4%)
dermatitis	0	1 (0.4%)
eye pain	0	1 (0.4%)
calification of breast tissue	0	1 (0.4%)

Appendix H

Reference: **8.5.2 Clinical Laboratory Findings**

On Feb 6, 1991 the Division requested full case reports for all patients treated with zolpidem in the Lorex program who experienced a potentially clinically significant laboratory abnormality (PCSA). The firm responded on Feb 18, 1991 with a 26-volume submission. A line listing of these patients follows.

Lorex Program

Study	Investigator	Patient	Volume
LSH01	Weintraub		*1*
LSH02	Roth		*1*
			2
			2
LSH03	Scharf		*3*
			4
LSH04	Cohn		*6*
			6
LSH06	Leese		*6*
LSH12	Mendels		*7*
			7
			7
			7
			7
			7
			8
			8
			8
			8
	Scharf		*9*
			10
			10
	Thorpy		*11*
	Weiss		*11*
			11
LSH13	Jasinski		*12-13*
LSH14	Jasinski		*14-15*
			20-21
LSH	Roth		*24*
LSH	Kann		*25*
	Leppik		*26*
			26
	Lahmeyer		*26*

Appendix I

Reference: **8.5.7 Drug-disease Interactions.**

The author's discussion of the pathophysiology of snoring, with a description of an empirical grading system, is taken from the introduction to the report, "Controlled polysomnographic study of the effects of benzodiazepine and non-benzodiazepine hypnotics in obstructive sleep apnea patients." *[Vol 114/0008]*

1. INTRODUCTION

During the late 70s Lugaresi and coworkers first outlined the hypothesis that snoring was not simply a trivial and socially disturbing sleep habit, but in some patients it could be the forerunner of Obstructive Sleep Apnea Syndrome (1).

An epidemiologic study, launched by the Lugaresi group at the San Marino Republic Hospital in 1980, indicated a 19% prevalence of snoring within the general population (24.9% among males and 13.8% among females). However, whilst at the age of 20 only 10% of males and 5% of females complained of habitual snoring, a steep increase occurred with age and in the 7th decade of life 60% of males and 40% of females referred on this disturbance (2).

A close association between heavy snoring and increased incidence of cardiovascular disorders was also revealed (2, 3, 4, 5).

Heavy snorrers underwent a systematic polysomnographic study in a sleep laboratory to characterize the features of the disturbance. Snoring is due to a reduction in the diameter of the upper airways; this stenosis increases the turbulence of the inspired stream of air, causing vibration of the soft tissues of the pharynx. The phenomenon occures episodically in almost anyone; in some, however (depending on anatomical and functional features), it occurrs over prolonged periods of the night. In some of these heavy snorrers, higher degrees of throat stenosis also occurs sometimes, at first transiently and mainly following consumption of alcohol or drug abuse, following this the frequency increases eventually inducing obstructive apnea syndrome.

Although the pathophysiological connection between the 2 phenomena remains as yet unknown, Lugaresi and coworkers proposed, in an attempt to cover the whole spectrum of this morbid process, the name "the heavy snorrer disease" (6), along with the following classification of the severity of disturbance :

- stage 0 consists of heavy snoring with sporadic apneas confined to stage 1-2 NREM and REM sleep;

- in stage 1 apneas occur almost continuously during stage 1-2 NREM and REM sleep, but the body position modifies their frequency (worse when lying on the back than on the side);
- in stage 2 apneas occur during all the sleep stages and are not influenced by the body position;
- in stage 3, as well as apnea-related phasic falls in arterial oxygen saturation (PaO_2), tonic long-lasting falls occur during REM sleep and alveolar hypoventilation also persists during wakefulness.

Apneas in turn prevent a deep stable sleep, and increase the percentage of stage 1-2 NREM sleep, i.e. the sleep stages in which apneas are more likely to occur; a vicious circle is therefore put into play which sustains and accentuates the disturbance.

Patients therefore frequently complain of sleep fragmentation and sometimes of difficulty in sleep onset and maintenance (DIMS A4a) (7).

The San Marino study indicated that nearly 20% of heavy snorrers complain of insomnia and many receive hypnotic drugs. However the administration of hypnotic drugs, as well as aging, overweight and alcohol consumption can cause the transition to a higher stage of the syndrome, bolstering the aformentioned vicious circle.

In 1981 Mendelson reported the case of an insomniac patient who showed sleep apneas after the administration of flurazepam 30 mg (8); he was a heavy snorrer with otherwise normal cardiac and respiratory findings when awake. Several other observations have indicated the potential problems associated with the administration of hypnotic drugs to patients suffering from sleep apnea (9, 10, 11, 12, 13, 14, 15).