NDA 19908

B10 Rv

DEC 12 1991

ZOLPIDEM
5 and 10 mg tablets
NDA 19-908
Reviewer: M. Daniel Gordin, Ph.D.

LOREX PARMACEUTICALS
Skokie, IL
Submission Date
June 28, 1991

[redacted] TYPE OF REVIEW: REVIEW OF AN SBA FOR ZOLPIDEM

The sponsor has submitted a SBA for zolpidem. The section pertaining to the biopharmaceutics portion on pages 76-81 will be reviewed.

1. On page 78, paragraph 4, the sponsor should indicate the types of proteins that zolpidem is bound to which are both acid alpha$_1$ glycoprotein and albumin plasma proteins and specify up to what concentration it is independent of dose.

2. On page 78, paragraph 7, the statment pertaining to dose proportionality was not reviewed; therefore, the accuracy of this statement cannot be verified.

3. On page 79, paragraph 9, the statment pertaining to the elderly should specify that the mean Cmax and AUC kinetic parameters were significantly increased by 50% and 64%, respectively, in the elderly compared to the younger adults.

4. Similarly on page 79, paragraph 9, the statment pertaining to cirrhotic patients should specify the significant increases in mean Cmax, AUC, and elimination half-life parameters in cirrhotic patients compared to healthy subjects. The Cmax and AUC values were 2 and 5 times higher with elimination half-life approximately 5 times longer in cirrhotic patients compared to healthy subjects.

5. On page 79, paragraph 10, pertaining to food effect, the sponsor should include the statment that mean tmax was prolonged (from 1.4 to 2.2 hrs) following the meal. The sponsor states that prolongation of tmax following a meal is not clinically significant; however, if one assumes that sleep onset is achieved faster with a shorter tmax, then the results of this study suggest that for faster sleep onset, zolpidem should be administered several hours following a meal, i.e. preferably on an empty stomach, when tmax is not prolonged.

6. On page 79, paragraph 10, the statment that the kinetic parameters were not altered in patients with renal impairment should include the increase in the apparent volume of distribution in such patients. While this data suggest that dose modification may be unnecessary in such patients, close monitoring is still indicated.

7. On page 80, paragraph 13, the first bioequivalency study (Study IGB09) involving 20 subjects failed to demonstrate bioequivalency between the to-be-marketed tablet and clinical capsule based on the 90% Confidence Interval Approach (Two One-Sided Tests Procedure)

(90% CI for Cmax 81-114 and for AUC 66-93) and their last statement that these formulations based on this study were considered bioequivalent is not true. Because of this study, the sponsor subsequently submitted Study LSH27 (submitted February 4, 1991) involving 30 subjects which demonstrated bioequivalency between the clinical capsule and the to-be-marketed tablet (90% CI for Cmax 92-113, for AUC 101-120).

RECOMMENDATION:

The Divsion of Biopharmaceutics has reviewed the SBA submitted by the sponsor for Zolpidem. Comments 1, 2, 3, 4, 5, 6, and 7 above should be addressed by the sponsor and the should be incorporated in the SBA.

Please convey Comments 1, 2, 3, 5, 6, and 7 to the sponsor.

M. Daniel Gordin

M. Daniel Gordin, Ph.D.
Pharmacokinetics Evaluation Branch

RD Initialed by Nicholas Fleischer, Ph.D. for 11/27/91
FT Initiated by Nicholas Fleischer, Ph.D. for 11/27/91

cc: NDA 19-908, HFD-120, HFD-426 (Gordin), Reviewer, Drug, Chron, HFD-19 (FOI).

\120\Zolpidem.SBA

Major Clinical Biopharmaceutic Studies:

ata on the pharmacokinetics of zolpidem were derived from 24

pharmacokinetic trials involving 352 subjects and from blood and plasma level measurements obtained during 12 Phase I pharmacodynamic and six Phase II and Phase III clinical trials in 320 subjects. All trials with the exception of two Phase I pharmacokinetic trials and one Phase II trial were conducted by Synthelabo. In all trials, the concentration of zolpidem was measured by a validated high pressure liquid chromatography assay using fluorometric detection. T1

Single Dose Studies

Eight pharmacokinetic trials were conducted in which a total of 104 normal volunteers (69 male, 35 female) 19 to 45 years of age received a single 20 mg dose of zolpidem. Principal demographic and pharmacokinetic parameters from these eight studies are summarized in Table 19. T2

TABLE 19

PHARMACOKINETIC PARAMETERS AFTER A SINGLE 20 MG ZOLPIDEM DOSE

	AGE (YRS)	WEIGHT (KG)	Cmax (NG/ML)	Tmax (HRS)	T 1/2 (HRS)	AUC (NG/ML.HR)
No. Subj.	104	104	65	65	104	104
Mean	24.5	64.6	260	1.8	2.4	996
SEM	0.5	1.0	16	0.3	0.2	59
Minimum						
Maximum						

The ranges in these parameters indicate there is inter-individual variability in zolpidem's pharmacokinetics. T3

Following oral administration, zolpidem is excreted according to a one-compartment model. Following oral or intravenous T4

administration, the amount of zolpidem excreted unchanged in the urine is less than 0.1%, indicating that zolpidem clearance is essentially metabolic. In a radio-labeled zolpidem study, three metabolic routes were identified. Only one circulating plasma metabolite has been identified, and it is pharmacologically inactive. Zolpidem is approximately 92% protein bound, and protein binding is not affected by salicylic acid, chlorpromazine, haloperidol, imipramine, or desipramine. Zolpidem is detectable in human breast milk following a single oral 20 mg dose. T14

Multiple Dose Studies

Twelve healthy volunteers received 20 mg zolpidem nightly for two weeks. Mean peak plasma concentrations, mean AUCs, and mean elimination half-lives after the first dose were not significantly different from those following 15 nights of dosing. T15

Dose Proportionality

Single doses of zolpidem 10 and 20 mg tablets were administered to 20 healthy volunteers. Cmax after 20 mg was proportional to Cmax after 10 mg, while AUC after 20 mg was slightly more than twice that after 10 mg. T16

In a second study, zolpidem 2.5, 5, 7.5, 10, and 20 mg were given to 12 subjects. Mean serum concentrations 9.5 hours after administration increased in a linear fashion. T17

In a third study, single zolpidem doses of 2.5, 5, 10, 20, and 40 mg were given to 48 subjects. Dose proportionality was exhibited across the dose range studied with respect to AUC_{0-12}, AUC_{0-inf}, and Cmax. Oral clearance, apparent volume of distribution, and elimination half-life were equivalent for all doses studied, providing further evidence of the linearity of the pharmacokinetics T18

of zolpidem.

Variations in Pharmacokinetics

In adults over 60 years of age, zolpidem's elimination half-life averaged 2.9 hours, approximately one-half hour longer than in 19-45 year olds. Cmax and AUC also increased with age. Children had a zolpidem clearance approximately three times greater than that in young adults, resulting in Cmax and AUC equivalent to those in adults despite the higher mg/kg dose. Females given zolpidem had a Cmax and AUC approximately 25% higher than males when corrected for weight. Nighttime administration of zolpidem resulted in lower Cmax and longer Tmax; however, AUC was unchanged. In eight patients with alcoholic cirrhosis, zolpidem's kinetics were described by a two-compartment model with elimination half-lives of 1.4 ± 0.1 and 9.9 ± 2.9 hours, respectively. TT9

Small but significant changes in the pharmacokinetics of zolpidem (i.e., reductions in AUC and Cmax) were seen when the drug was administered with food; however, the small magnitude of the reductions and the narrowness of the 95% confidence interval limits indicate that the true differences are expected to be relatively small and predictable, and do not suggest a need for special labeling. Pharmacokinetic parameters were not altered in patients with severe renal impairment, and zolpidem was found to be not dialyzable. TT10

Drug Interactions

Interaction studies were conducted with haloperidol, chlorpromazine, imipramine, cimetidine, ranitidine, and flumazenil; none of these drugs produced significant alterations in zolpidem pharmacokinetics. TT11

The effect of zolpidem on the pharmacokinetics of digoxin, imipramine, desipramine and antipyrine was also evaluated. Digoxin pharmacokinetics were not affected by zolpidem. A single dose of 20 mg zolpidem resulted in a small but significant reduction in imipramine Cmax; desipramine pharmacokinetics were not affected. Antipyrine elimination was not affected by 15 days of zolpidem administration, indicating zolpidem does not induce or inhibit hepatic enzyme activity. Concomitant administration of zolpidem and alcohol did not alter the blood levels of either drug. Although the combined effects of 20 mg of zolpidem and 3 ounces of ethanol have not been shown to be greater than the effects of zolpidem alone, patients should be cautioned against the ingestion of alcohol with zolpidem due to the potential additive effects. TT12

Bioequivalence

The bioequivalency of zolpidem capsule and tablet dosage forms was determined. Twenty (20) healthy volunteers each received three single doses using (1) a 10 mg capsule, (2) a 10 mg tablet, and (3) a 20 mg tablet. These subjects also received a 30-minute intravenous infusion of 8 mg zolpidem. The 10 and 20 mg tablets had absolute bioavailabilities of 66.6% and 70.2%, respectively. The bioavailability of the capsule was 67.5%. There were no statistically significant differences in dose-adjusted AUC among the three groups, and Westlake intervals were less than 20%. These formulations were considered bioequivalent. TT13

In a second study, the pharmacokinetics and relative bioavailability of liquid and solid (capsule and tablet) forms of zolpidem were determined. Single nighttime 10 mg oral doses were administered to 31 subjects. Zolpidem tablets and capsules were fully bioavailable relative to the liquid reference in terms of rate and extent of absorption, and the tablet and capsule forms were bioequivalent to each other. TT14

Summary of the pertinent pharmacokinetic findings:

Zolpidem is a hypnotic with a mean plasma half-life of 2.4 ± 0.2 (± SEM) hours. The half-life is slightly longer in females than in males, and is increased to 2.9 ± 0.2 hours in subjects 60 years of age and older. In the range of doses studied (2.5 to 40 mg), zolpidem demonstrates linear pharmacokinetics. Relative single-dose bioavailability of zolpidem is 99%. Following oral administration, zolpidem is rapidly absorbed, attaining peak concentrations in blood in 0.5 to ? hours. Peak concentrations are increased by approximately 50% in elderly subjects (> 70 years of age). The elimination of zolpidem after single doses is prolonged in patients with cirrhosis (half-life = 9.9 ± 2.9 hours). Zolpidem dose should be modified accordingly in these patients.

π 15

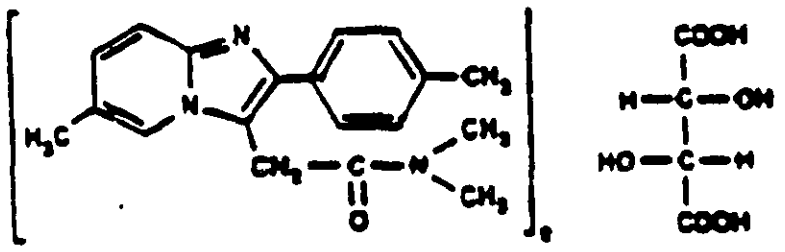
VI. PROPOSED PACKAGE INSERT

STILNOX®
(zolpidem tartrate)

DESCRIPTION

STILNOX® (zolpidem tartrate), is a non-benzodiazepine hypnotic of the imidazopyridine class and is available in 5 mg and 10 mg strength tablets for oral administration.

Chemically, zolpidem is N,N,6-trimethyl-2-p-tolyl-imidazo[1,2-a]pyridine-3-acetamide L-(+)-tartrate (2:1). It has the following structure:



JUL 17 1991

ZOLPIDEM TARTRATE
5 and 10 mg Tablets
NDA 19-908
Reviewer: M. Daniel Gordin, Ph.D.

LOREX PHARMACEUTICALS
Skokie, IL
Submission Date
June 28, 1991

[redacted]

REVIEW OF A BIO-STUDY

BACKGROUND:

This study was recently submitted as an addendum to the original NDA submission zolpidem tartrate. It is a bioequivalency study, the review of which follows.

STUDY TITLE: Bioequivalence of Zolpidem Administered as a Capsule or Tablet to Healthy Male Adults (LSH91)

INVESTIGATOR: Kenneth Lasseter, M.D.
Clinical Pharmacology Associates
2060 N-W 22nd Avenue
Miami, Florida 33142

OBJECTIVE: To establish bioequivalence between 10 mg clinical capsules and 2x5 mg to-be-marketed tablet and 10 mg to-be-marketed tablets.

FORMULATION:

5.0 mg to-be-marketed tablet	PT-233-90*
10.0 mg to-be-marketed tablets	PT-232-90*
10.0 mg clinical capsules	KLZ05-03C**

* Batches from full production scale lots of 1,250,000 tablets manufactured at Searle production facility in Puerto Rico. ** Manufactured in France

STUDY DESIGN:

This was an open-label, 3-period, 3-treatment, randomized, balanced Latin square design, with successive single-dose zolpidem treatment periods separated by a minimum 7-day washout period in healthy male adults. Subjects received the doses at night-time 5 hr after a light meal, the same for all 3 periods. A total of 36 subjects were randomized, and 33 subjects completed the study (20 Caucasian, 8 Blacks, 7 Hispanic, 1 unspecified Other). Blood samples were obtained at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, and 12 hrs post dosing.

ASSAY:

The analytical determination of zolpidem concentrations in plasma samples was done according to the validated method developed by Hazleton Laboratories America. It is acceptable.

1. Sensitivity: The limit of quantitation (LOQ) was [redacted] ng/mL. The relative standard deviation (RSD) (n=6) of the peak height ratios was 8.3% and that of the measured concentrations from the nominal value was 0.2%.

2. Linearity: The calibration curves for zolpidem in plasma were linear in the concentration range from [redacted] ng/mL, with correlation coefficients greater than 0.9995. Calibration standards of 1, 2, 10, 20, 50, 100 and 400 ng/mL were used. From the subject sample analyses, the relationship between peak height ratio and concentration for zolpidem was also linear in the curve ranges from [redacted] ng/mL, with correlation coefficients which exceeded 0.9900.

3. % Accuracy: The accuracy of the method was determined by comparing the means of the measured concentrations of the controls with their nominal concentrations. Data from the methods validation report document that all of the daily mean (n=6) and overall mean (n=18) values were within 4% of their expected values.

4. Precision: From the methods validation report, the within-day precision of the method was determined from the relative standard deviation (RSD) of six replicate analyses of each of the 3 control pools. The overall precision of the method was determined from the RSD of 18 analyses of the 3 control pools over 3 days. The within-day precision ranged from 0.9% to 2.7% RSD (n=6) for zolpidem at all 3 qc levels. The overall precision was 2.3%, 1.9% and 1.1% RSD (n=18) for the [redacted] ng/mL zolpidem controls, respectively. From the subject sample analytical report the variability of the back-calculated concentrations of the calibration standards ranged from 0.9% to 6.4% for zolpidem. The between-day precision was determined at levels of [redacted] ng/mL in replicate analyses (n=23, n=23, and n=23, respectively). The between-day variability did not exceed 6.4%.

5. Specificity: No interfering peaks were found at the retention times of zolpidem or the internal standard for the pools tested.

RESULTS:

TABLE. The mean zolpidem PK parameters (N=33) and the result of the 90% Confidence Intervals. ^(ng/hr/mL) ^^(ng/ml)

	Mean (%CV) Results			90% C.I.		
	2x5 mg Tablet	1x10 mg Tablet	1x10 mg Capsule	2x5 mgTab/ 10 mg Tab	10 mg Tab/ 10 mg Cap	p value
$AUC^{\wedge}_{0-12}$	460.9 (60)	439.9 (52)	446.6 (54)	86-104	89-107	0.54
$AUC^{\wedge}_{0-inf}$	499.8 (64)	479.3 (54)	484.7 (58)	86-106	89-109	0.65
C_{max}^^	115.6 (61)	111.6 (52)	112.7 (54)	83-110	85-112	0.88
T_{max}(hr)	1.6 (65)	1.9 (70)	1.5 (76)	90-142	95-151	0.53
$T_{1/2}$(hr)	2.6 (33)	2.8 (31)	2.7 (32)	--	--	0.49

COMMENT:

1. The PK parameters demonstrate that at a comparable 10 mg dose, the different tablet and capsule formulations do not differ significantly for AUC, Cmax, tmax and half-life between any of the three formulations.

2. Based on the results of the 90% Confidence Interval (Two One-sided Tests Procedure), this study 1) demonstrated bioequivalence between the zolpidem 2x5 mg tablets and 1x10 mg tablets and 2) between the 10 mg to-be-marketed tablet from a full scale production batch manufactured in Puerto Rico and 10 mg clinical capsule formulations.

RECOMMENDATION:

The Division of Biopharmaceutics (DB) has reviewed the study which for Zolpidem tablets which was submitted June 28, 1991. Based upon the review of the submitted bioavailability/pharmacokinetic information and data, the Division of Biopharmaceutics concludes that the sponsor has demonstrated bioequivalency between the 10 mg and 5 mg to-be-marketed tablets and the clinical capsule.

M. Daniel Gordin

M. Daniel Gordin, Ph.D.
Pharmacokinetic Evaluation Branch

RD Initialed by John P. Hunt 7/16/91
FT Initialed by John P. Hunt 7/16/91

cc: NA19-908, HFD-120, HFD-426 (Gordin), Reviewer, Drug, Chron, HFD-19 (FOI), E.

APPENDIX F.2

DEMOGRAPHIC AND PATIENT CHARACTERISTICS

LSH91

VOLUME 2 of 7

JUNE 28, 1991 SUBMISSION

Appendix F.2
Data Listing - Patient Characteristics
Study: LSH91

Subject Number	Age (yr)	Gender	Race	Height (cm)	Weight (kg)	Sitting Systolic BP (mmHg)	Sitting Diastolic BP (mmHg)	Sitting Pulse Rate (bpm)	Sequence
2	26	M	Caucasian	180.3	83.6	112	70	80	2
5	31	M	Caucasian	182.9	77.3	122	72	72	5
6	30	M	Caucasian	167.6	66.8	108	66	64	4
10	37	M	Caucasian	185.4	89.1	110	74	74	3
12	37	M	Black	167.6	75.0	128	86	70	6
13	31	M	Caucasian	182.9	88.2	126	74	68	1
** 18	37	M	Caucasian	182.9	78.2	124	88	64	6
24	37	M	Hispanic	167.6	64.5	110	78	78	5
25	39	M	Caucasian	178.2	72.3	120	84	72	3
32	28	M	Black	182.9	63.6	112	68	78	2
34	31	M	Caucasian	182.9	81.4	116	70	80	6
36	25	M	Hispanic	185.4	79.1	112	74	70	3
** 37	38	M	Caucasian	175.3	71.4	138	88	68	1
38	42	M	Caucasian	188.0	84.5	128	80	72	2
39	32	M	Caucasian	165.1	64.1	120	86	76	5
42	46	M	Caucasian	185.4	91.8	128	84	80	5
43	44	M	Caucasian	177.8	83.2	126	88	60	6
** 45	22	M	Black	172.7	69.1	106	72	66	1
49	36	M	Caucasian	157.5	65.0	112	70	70	4
53	29	M	Black	175.3	85.9	100	70	64	1
57	33	M	Caucasian	177.8	72.7	118	74	72	4
58	32	M	Caucasian	180.3	73.4	114	72	68	2
59	36	M	Black	175.3	89.1	124	84	64	2
61	45	M	Caucasian	177.8	88.2	122	84	72	1
62	41	M	Other	172.7	75.9	128	80	64	6
63	25	M	Black	180.3	80.9	112	80	72	3
64	34	M	Black	177.8	78.4	134	82	72	4
67	32	M	Caucasian	188.3	76.4	122	74	68	5

Appendix F.2
Data Listing - Patient Characteristics
Study: LSH91

Subject Number	Age (yr)	Gender	Race	Height (cm)	Weight (kg)	Sitting Systolic BP (mmHg)	Sitting Diastolic BP (mmHg)	Sitting Pulse Rate (bpm)	Sequence
70	23	M	Hispanic	167.6	73.2	124	78	68	4
73	25	M	Hispanic	175.3	65.0	108	64	62	4
74	27	M	Hispanic	170.2	65.0	110	66	60	3
76	25	M	Caucasian	172.7	64.5	100	76	64	1
78	26	M	Black	182.9	78.2	130	80	80	2
79	46	M	Hispanic	162.6	64.1	110	70	62	6
81	27	M	Caucasian	172.7	78.2	120	82	68	3
82	34	M	Hispanic	170.2	78.2	110	80	74	5

*** Did not complete trial

Sequence Code: 1 = 10mg Cap, 5mg Tab, 10mg Tab
2 = 10mg Tab, 10mg Cap, 5mg Tab
3 = 5mg Tab, 10mg Tab, 10mg Cap
4 = 10mg Tab, 5mg Tab, 10mg Cap
5 = 10mg Cap, 10mg Tab, 5mg Tab
6 = 5mg Tab, 10mg Cap, 10mg Tab

APPENDIX A.1

LISTING OF ZOLPIDEM PLASMA CONCENTRATION BY SUBJECT

LSH91

6 Pages

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APPENDIX A.3

PHARMACOKINETIC PARAMETER ESTIMATES BY SUBJECT

LSH91

6 Pages

Redacted

SEP 27 1991

ZOLPIDEM TARTRATE
5 mg and 10 mg tablets
NDA 19-908
Reviewer: M. Daniel Gordin, Ph.D.

[redacted]

LOREX PHARMACEUTICALS
Skokie, ILL
Submission Dates:
January 26, 1989
February 4, 1991
March 15, 1991
April 17, 1991

SUMMARY FOR ZOLPIDEM TARTRATE

Zolpidem is an imidazopyridine hypnotic agent indicated for transient, short-term and chronic insomnia. Its PK profile is characterized by rapid absorption, a short half-life, and metabolic elimination without active metabolites. The following studies were reviewed by the Division of Biopharmaceutics (Review Stamp Date: July 17, 1991)

a) Two bioequivalency studies; the results of the second (submitted February 1991) demonstrated BE between the 10 mg to-be-marketed tablet and the 10 mg clinical capsule.
b) A multiple dose and effect on antipyrine study (20 mg qd pm dosing for 15 days) which showed zolpidem did not accumulate and antipyrine kinetics used as an indication of hepatic induction did not change.
c) A dose proportionality study covering the therapeutic range of 5, 10, 15, and 20 mg which showed linearity.
d) A C-14 zolpidem labelled mass balance study.
e) A food effect study which demonstrated a slight food effect on the kinetics of zolpidem.
f) Special population kinetics studies of zolpidem in elderly versus younger adults, males versus females, liver impaired patients, renal impaired patients, children, and obese subjects.
g) Single dose drug interaction studies between zolpidem and imipramine, alcohol, flumazenil, chlorpromazine, haloperidol, cimetidine, and ranitidine.
h) Protein binding and breast clearance of zolpidem in humans.

The Division of Biopharmaceutics concluded that based on the reviewed studies, the sponsor fulfilled the Division of Biopharmaceutics requirements for NDA 19-908, zolpidem tartrate.

M. Daniel Gordin

M. Daniel Gordin, Ph.D.
Pharmacokinetics Evaluation Branch

RT/FT Initialed by John P. Hunt JPH 9/24/91

cc: NA19-908, HFD-120, HFD-426 (Gordin), Reviewer, Drug, Chron, HFD-19 (FOI).

\120\Zolpidem.Sum

JUL 17 1991

ZOLPIDEM TARTRATE
5 mg and 10 mg tablets
NDA 19-908
Reviewer: M. Daniel Gordin, Ph.D.

[redacted]

LOREX PHARMACEUTICALS
Skokie, ILL
Submission Dates:
January 26, 1989
February 4, 1991
March 15, 1991
April 17, 1991

REVIEW OF A NEW MOLECULAR ENTITY

TABLE OF CONTENTS page

I. RECOMMENDATION:

A. The Division of Biopharmaceutics (DB) has reviewed NDA 19-908 which was first filed January 26, 1989 for Zolpidem tablets. Based upon the review of the submitted bioavailability/pharmacokinetic information and data, the Division of Biopharmaceutics concludes that the sponsor has adequately described the pharmacokinetics and bioavailability of zolpidem.

B. Since the results of Study IFR12 in patients with renal disease were following intravenous administration of zolpidem rather than a tablet, a definite conclusion regarding the lack of effect of renal disease on the pharmacokinetics of zolpidem following an oral dose cannot be made. A study in renal disease patients in which a tablet is administered is suggested as a Phase IV study.

C. The following is recommended for dissolution:
USP Apparatus 2 (paddle) method at 50 RPM
900 ml of 0.01 N HCl (pH 2) at 37°C.
Specification: Not Less Than [redacted]

Please convey the Recommendation, Labeling Comments (page 39-40), Dissolution Procedure and Specification to the sponsor. The sponsor should re-submit the package insert for review when all changes have been incorporated.

M. Daniel Gordin

M. Daniel Gordin, Ph.D.
Pharmacokinetic Evaluation Branch

RD Initialed by John P. Hunt June 23, 1991
Biopharmaceutics Day: July 15, 1991. J. Collins, Ph.D., H. Malinowski, Ph.D., J. Hunt, P. Hepp, Pharm.D., R. Baweja, Ph.D.

FT Initialed by John P. Hunt 7/16/91

cc: NA19-908, HFD-120, HFD-426 (Gordin), Reviewer, Drug, Chron, HFD-19 (FOI), DI, A, G, F, E.

\120\Zolpidem.Rev

1 Page(s)

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II. BACKGROUND:

Zolpidem is an imidazopyridine hypnotic agent being developed for transient, short-term and chronic insomnia. Its PK profile is characterized by rapid absorption, a short half-life, and metabolic elimination without active metabolites. The following studies were reviewed:

a) Two bioequivalency studies; the results of the second (submitted February 1991) demonstrated BE between the 10 mg to-be-marketed tablet and the 10 mg clinical capsule.
b) A multiple dose and effect on antipyrine study (20 mg qd pm dosing for 15 days) which showed zolpidem did not accumulate and antipyrine kinetics used as an indication of hepatic induction did not change.
c) A dose proportionality study covering the therapeutic range of 5, 10, 15, and 20 mg which showed linearity.
d) A C-14 zolpidem labelled mass balance study.
e) A food effect study which demonstrated a slight food effect on the kinetics of zolpidem.
f) Special population kinetics studies of zolpidem in elderly versus younger adults, males versus females, liver impaired patients, renal impaired patients, children, and obese subjects.
g) Single dose drug interaction studies between zolpidem and imipramine, alcohol, flumazenil, chlorpromazine, haloperidol, cimetidine, and ranitidine.
h) The protein binding and breast clearance of zolpidem in humans

A. DOSAGE AND ADMINISTRATION:

The following is the recommended dosage and administration in the proposed labeling.

> The recommended dose for transient short-term and chronic insomnia is 10 mg immediately before bedtime. Subsequent doses may be adjusted based on response. Dosage should not increased by more than 5 mg increments with total dose not to exceed 20 mg.
>
> Elderly and/or debilitated patients and patients with hepatic insufficiency may be especially sensitive. An initial 5 mg dose is recommended in these patients. The total dose should not exceed 10 mg.

B. FORMULATION:

The list of ingredients for the 5 and 10 mg to-be-marketed tablets is attached. The 5 and 10 mg tablets are considered to be proportionally similar since they contain the same amount of ingredients except for the drug itself.

III. PHARMACOKINETIC/BIOAVAILABILITY

A. ANALYTICAL METHODOLOGY:

Zolpidem plasma concentrations for the original PK studies were assayed by the following method. Plasma samples were extracted for zolpidem and internal standard with diethyl ether. The extract was dried and the residue reconstituted with mobile phase and analyzed by HPLC utilizing a CH_3CN/phosphate buffer mobile phase resulting in 2 distinct peaks. Retention times for zolpidem and the internal standard were 3.6 and 4.6 minutes, respectively. A standard curve utilizing concentrations of [redacted] ng/ml zolpidem was shown to be linear over the range with a correlation coefficient of 0.998 was obtained. Reproducibility was determined by analyzing the zolpidem standards at least 5 times resulting in coefficients of variations of <16% at [redacted] ng/ml, 3.9% at [redacted] ng/ml and 3.8% at [redacted] ng/ml. The assay is acceptable.

B. PK STUDIES:

In a majority of studies, a capsule was used as the dosage form. Since the to-be-marketed dosage form is a tablet, the first 2 studies reviewed are bioequivalence studies between the to-be-marketed tablet and the clinical capsule.

TITLE: STUDY OF THE RELATIVE BIOAVAILABILITY OF TWO ORAL FORMULATIONS AND THE ABSOLUTE BIOAVAILABILITY OF THE FINAL FORMULATION OF ZOLPIDEM (Study IGB09)

INVESTIGATOR: S.J. Warrington, MD
London, England

OBJECTIVES:

1. To compare the relative bioavailability of zolpidem capsule and the tablet which is the final formulation.
2. To assess linear pharmacokinetics between the 10 and 20 mg tablets.
3. To determine the absolute bioavailability of the coated tablet formulation.

FORMULATIONS

Treatment A:	10 mg clinical capsule	LP 12607
Treatment B:	8 mg IV infusion 1 mg/ml	LP 12295
Treatment C:	20 mg Not to-be-marketed tablet	LP 12572E
Treatment D:	10 mg to-be-marketed tablet	LP 12465E

DESIGN:

This was an open, four-way crossover design involving 20 subjects (10 male, 10 female,age 19-31). After a 12 hr fast, the treatments were administered with 150 ml of water. Treatment B was

administered as a 30 min intravenous infusion. A breakfast was given 2 hrs following administration. The subjects were crossed to an alternate formulation after a one wk washout. Samples of blood were removed at 0, 15, 30, 45 min, 1, 2, 3, 4, 6, 8, 10, 12, 16 and 24 hrs following oral administration. For the intravenous dose, samples were removed at 0, 30, 40, 50, 60, 90 minutes, 3, 4, 6, 8, 10, 12, 16, and 24 hrs post-dose. The plasma samples were stored at -20°C until time of analysis.

RESULTS:

The individual data are found Volume 1.41 of the submission.

Table. The mean (%CV) PK parameters obtained following a single oral dose of 10 mg capsule (CAP), 10 and 20 mg tablets (TAB). The 90% CI results are the comparison between the 10 mg capsule and the 10 mg tablet. *(ng.h/ml)

	10 mg CAP	20 mg TAB	10 mg TAB	90%CI	Result
Cmax (ng/ml) Range	143 (55)	290 (34)	139 (39)	81-114	pass
AUC(inf)* Range	453 (81)	861 (59)	362 (62)	66-93	fail
tmax (hr) Range	1.2 (74)	1.0 (89)	1.0 (89)	x	
Half-life (hr) Range	1.7 (53)	1.8 (50)	1.5 (30)	x	
%F	67.5 (34)	70.2 (36)	66.6 (28)	x	

Table. The mean PK parameters following an 8 mg intravenous infusion of zolpidem.

	Cendinf	half-life	AUC	Clt(l/h/kg)	Vd(l/kg)
Mean	197	1.7	483	0.26	0.54
%CV	21	24	49	48	15

COMMENTS:

1. The results of this study show a large degree of intersubject systemic variability for zolpidem as evident by the large %CV for AUC (81%, 59%, and 61%).

2. The absolute systemic bioavailability of zolpidem was 67.5%, 66.6%, and 70.2% for the 10 mg capsule, 10 mg tablet, and 20 mg tablet respectively.

3. An objective of this study was to establish bioequivalency between the to-be-marketed 10 mg tablet and the 10 mg clinical capsule. Based on the Agency's 90% Confidence Interval Approach (Two One-sided Test Procedure), this study failed to demonstrate equivalency between the to-be-marketed tablet and clinical capsule. The results indicate that the AUC(0-inf) between the two are not within the critical range of 80-120% (66-93%). Because of the results of this study, the sponsor submitted the results of a new bioequivalency study (February 4, 1991), the review of which follows.

STUDY TITLE: RELATIVE BIOAVAILABILITY OF LIQUID AND SOLID FORMS OF ORAL ZOLPIDEM IN NORMAL HEALTHY VOLUNTEERS (STUDY LSH27 - Date submitted February 4, 1991)

INVESTIGATOR: Russel M. Dixon, M.D.
Hazleton Laboratories of America
Madison, Wisconsin 53707

FORMULATIONS: 0.5% oral solution
10 mg to-be-marketed tablet
10 mg clinical capsule

OBJECTIVES:

1) To evaluate the pharmacokinetics and relative bioavailability of oral solution and solid forms of zolpidem in healthy male adults following oral administration of a single night-time 10 mg dose.

2) To evaluate the effects of food on the kinetics of a single night time dose of 10 mg zolpidem tablet.

STUDY DESIGN:

This was an open-label, five-period, single-dose, randomized balance design, consisting of 2 sequential crossovers involving 30 healthy male subjects. The first crossover consisted of 3 treatments (to-be-marketed 10 mg tablet, clinical capsule and 10 mg solution administered after an approximately 5 hr fast with 240 ml of water. The second crossover consisted of 2 treatments (the tablet administered in the absence or presence of food) administered at night-time. The 10 mg dose of zolpidem was administered 20 min after eating a bedtime meal which consisted of roast beef sandwich on whole wheat bread, banana, and skim milk. Each of the 5 treatments were separated by a minimum 7-day washout period. Blood samples were obtained at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, and 12 hrs.

ASSAY:

The analytical determination of zolpidem in plasma samples was by HPLC. Each analysis group of subject samples was analyzed with a set of calibration standards and pooled qc samples to assess the precision and accuracy of the method. A total of 2,250 subject plasma samples were analyzed. Specific details of the HPLC specifications are included in Appendix E.1 (pgs. 544-609), Volume 3 of 3, of the LSH27 final report submitted to the Zolpidem NDA (19-908) on February 4, 1991. Details on the assay procedures and specifications from both the methods validation report and the subject sample analyses are included here for completeness.

1. Sensitivity: The limit of detection (LOD) was defined as the minimum concentration that gives a detector response greater than three times the background noise level. The LOD for zolpidem was calculated to be [redacted] ng/ml. The limit of quantitation was set at [redacted] ng/ml of zolpidem in plasma. At that level, the relative standard deviation (RSD) (N=6) of the peak height ratios was 8.3% and that of the measured concentrations was 9.7%. The deviation of the mean of the measured concentrations from the nominal value was -0.2%. From the subject sample analysis the RSD of the calculated concentrations for the 78 analysis groups was 8.5% and the mean of the calculated concentration was 6% from the nominal concentration.

2. Linearity: The calibration curves for zolpidem in plasma were linear in concentration range from [redacted] ng/ml with correlation coefficients greater than 0.9995.

3. % Accuracy: The accuracy of the method was determined by comparing the means of the measured concentrations of the controls described above with their nominal concentrations. All of the daily mean (N=6) and overall mean (N=18) values were within 4% of their expected values. For the subject sample analysis the accuracy of the method was also quite good. The means of the controls fell within 2% of their nominal concentrations at all 3 control levels [redacted] ng/ml). The means of the calculated concentrations of the calibration standards were all within 6% of their nominal concentrations for all the standards.

4. Precision: The within-day precision of the method was determined from the RSD of 6 replicate analyses of each of 3 control pools. The overall precision of the method was determined from the RSD of 18 analyses of the 3 control pools over 3 days. The within-day precision of the method ranged from 0.9% to 2.7% RSD (N=6) for zolpidem at all 3 quality control levels. The overall precision was 2.3%, 1.9%, and 1.1% RSD (N=18) for the 3, 30 and 300 ng/ml zolpidem controls, respectively. The precision of the method for subject sample analysis was assessed from the RSD of the controls and calibration standards and duplicate sample analysis. The RSD of the controls for the 78 analysis groups did not exceed 5.9% at any of the 3 quality control levels.

5. Specificity: No interfering peaks were found at the retention times of zolpidem or the internal standard for the pools tested. This data is shown in Figures 4 (pg. 587) and 10 (pg. 591) of Appendix E.1. The assay is acceptable.

RESULTS:

The 90% confidence interval results are between the 10 mg clinical capsule and 10 mg to-be-marketed tablet.

TABLE. The mean pharmacokinetic parameters of 10 mg zolpidem (N=30).

	Solution	Tablet	Capsule	p-value	90%CI
AUC(0-12)	396.75	384.63	352.96	0.733	100-118
%CV	60%	59%	51%		
AUC (inf)	421.43	415.88	374.18	0.681	101-120
%CV	65%	66%	56%		
C_{max}(ng/ml)	96.99	95.38	92.61	0.204	92-113
%CV	40%	46%	44%		
T_{max}(hr)	0.95	1.77	1.40	0.122	101-156
%CV	76%	63%	68%		
T1/2 (hr)	2.25	2.31	2.25	0.932	
%CV	37%	38%	30%		

TABLE. The mean food vs fasting zolpidem pharmacokinetic parameters.

	Tablet-fasted	Tablet-food	p-value^
AUC^^(0-12)	398.9	344.0	0.001
%CV	56	52	
AUC^^(inf)	427.9	367.3	0.003
%CV	62	56	
Cmax (ng/ml)	100.1	75.5	0.003
%CV	42	43	
tmax (hr)	1.4	2.2	0.008
%CV	66	72	
half-life (hr)	2.3	2.2	0.112
%CV	39	31	

^Overall treatment comparison (ANOVA).^^(ng.h/ml)

COMMENT:

1. Consistent with the results of other studies is the large degree of intersubject variability in the kinetics parameters of zolpidem tablets as evident by the large %CV for AUC and Cmax. Zolpidem is a highly variable drug.

2. The determination of the relative bioavailability of 10 mg zolpidem tablet to the oral solution shows that the tablet has a relative bioavailability of 97%.

3. From the comparison between food vs fasting, the AUC and Cmax values were significantly lower (15% and 25% for AUC and Cmax respectively) while tmax was found to be significantly increased (1.4 to 2.2 hrs) when zolpidem was administered 20 min after a meal. The half-life was unchanged. It is not known if the change in kinetics would indicate any significant change in the effect of the drug; however, the results of this food effect study should be included in the labeling.

4. Based on the Agency's 90% Confidence Interval Approach (Two One-sided Test Procedure), this study demonstrated equivalency between the 10 mg to-be-marketed tablet and the 10 mg clinical capsule following fasting PK dosing for Cmax and AUC. There was a 0.37 hr difference between tmax treatment means which was not significant by ANOVA analysis.

CONCLUSION:

The results of this study can be used to support the equivalency between the to-be-marketed tablet and the clinical capsule. The results of the food effect study should be added to the labeling.

TITLE: STUDY OF ZOLPIDEM KINETICS UNDERTAKEN IN MAN DURING REPEATED TREATMENT; EFFECT ON ANTIPYRINE CLEARANCE TEST (STUDY IFR24)

OBJECTIVES:

1. To determine the pharmacckinetic profile of zolpidem after a single dose and after repeated administration.

2. To use the antipyrine test to investigate any enzyme induction or inhibition phenomenon associated with repeated administration of zolpidem.

INVESTIGATORS: H. Albin; Clinical Pharmacology Dept; Pellegrin Hospital; 33076 Bordeaux, France

FORMULATION: 20 mg zolpidem tablet LP 12565-E
[Not to-be-marketed]

DESIGN:

This was a multiple dose study involving 12 healthy male volunteers (age 21-36). A 20 mg zolpidem tablet was administered once every 24 hrs for 15 days. Antipyrine (4 x 250 mg capsules) was administered on days 1 and 17. The dosing and sampling schedules were as follows:

Day 1, 4 x 250 mg capsules of antipyrine were administered at 7 am and saliva samples obtained at 3, 6, 9, 12, 16, 24 and 28 hrs.

Day 2, 20 mg zolpidem was administered at 9 pm. Blood samples were obtained at 0, 15, 30, 45 minute, 1, 2, 3, 4, 6, 8, 10, 12, 16, and 22 hrs.

Days 3-15, 20 mg of zolpidem was administered at 9 pm. On day 16, 20 mg zolpidem was administered at 9 pm and blood samples obtained at 0, 15, 30, 45 minute, 1, 2, 3, 4, 6, 8, 10, 12, 16, and 22 hrs.

Day 17, 4 x 250 mg antipyrine were administered at 7 am. Saliva samples were obtained at 3, 6, 9, 12, 16, 24, and 28 hrs.

RESULTS:

The individual data are found in Volume 1.37. The statistical analysis was determined by ANOVA.

Table. The mean (%CV) zolpidem pharmacokinetic parameters after a 20 mg tablet on day one (D1) and on day 15 (D15). (ng*hr/ml)*

	D1	D15	ANOVA
Cmax (ng/ml)	193 (38)	200 (45)	NS
AUC (0-22)*	782 (76)	699 (63)	x
AUC (inf)*	792 (76)	708 (63)	NS
Half-life (hrs)	1.9 (40)	1.8 (43)	NS
tmax (hr)	2.2 (45)	2.3 (43)	NS
Cmin (ng/ml)	1.4	1.1	NS

Table. The mean half-life of salivary antipyrine after a 20 mg zolpidem tablet on day 1 and after repeated administration of zolpidem.

	D1	D17
Half-life (hrs)	12.1	10.7
%CV	41	32

COMMENTS:

1. Antipyrine was used as an indicator of hepatic induction following multiple dosing of zolpidem. There was a 1.4 hr difference between day 1 and day 17 mean anti-pyrine half-lives which were not significant by ANOVA analysis.

2. Zolpidem did not accumulate following multiple dosing as determined by first dose AUC to last dose AUC ratio. The accumulation of zolpidem is not anticipated because of its short half-life of approximately 2 hrs and with once-a-day dosing.

3. Althcugh the mean data for this product shows relatively good agreement in the pharmacokinetic parameters from Day 1 to Day 15 of dosing, there is a large degree of intra-subject variation from Day 1 to Day 15 as well as inter-subject variability. Inspection of individual subject data showed reductions as well as increases in the AUC and Cmax values of zolpidem on Day 15. It is not known if this reduction or increase in AUC and Cmax would indicate any significant change in the effectiveness of the drug. The Medical Officer is asked to evaluate if the effectiveness of zolpidem changes with time.

TITLE: ZOLPIDEM PHARMACOKINETICS AFTER REPEATED ORAL ADMINISTRATION IN MAN (STUDY IBE03)

INVESTIGATOR: J.M. Coupez, MD; Brussels, Belgium

OBJECTIVES: To determine the PK of zolpidem after multiple dose administration in healthy volunteers.

FORMULATIONS:

5 mg capsule	LP 12006
10 mg capsule	LP 12005
20 mg capsule	LP 11948

[Not to-be-marketed]

DESIGN:

This was a dose escalation study involving 16 adult male subjects who were divided into 2 groups of 8/group as follows:

Days	Group I	Group II
1, 2, 3, 4	5 mg	10 mg
5, 6, 7, 8	15 mg	20 mg

Groups I and II received 5 and 10 mg capsules respectively for days 1-4. At the end of day 4, the dose was increased to 15 and 20 mg for days 5-8. Each dose was administered in the AM before breakfast (hot chocolate and 2 croissants). (It was not indicated if the 15 mg dose was administered as 5 mg+10 mg capsules or 3x5 mg capsules). Samples of venous blood were taken on Day 1 at 0, 30 min, 1, 2, 4, 6, 8, 10, and 24 hrs after single dose administration of 5 and 10 mg and on Day 8 at 0, 30 min, 1, 2, 4, 6, 8, 10, 24, 28, and 32 hrs after multiple-dose administration of 15 and 20 mg.

RESULTS:

Individual data is found in Volume 1.38.

Table. The mean (%CV) PK zolpidem parameters for 5 and 10 mg on day 1 and for 15 mg and 20 mg on day 8 following multiple dose.

	5 mg SD	10 mg SD	15 mg MD	20 mg MD
Cmax (ng/ml)	52 (36)	170 (35)	130 (26)	286 (48)
AUC (0-24)	170 (44)	876 (59)	396 (42)	1503 (81)
half-life (hr)	3.9 (15)	2.7 (37)	5.4 (44)	2.7 (33)
tmax (hr)	1.2 (50)	0.5 (40)	1.2 (58)	0.5 (40)

COMMENTS:

1. Consistent with the results of previous studies, is large inter-subject variations in the AUC and Cmax. Based on the data, dose proportionality is lacking. Due to these results, the sponsor submitted the results of a new dose proportionality study (Submitted February 4, 1991), the review of which follows.

STUDY TITLE: DOSE PROPORTIONALITY OF ORAL ZOLPIDEM IN NORMAL HEALTHY VOLUNTEERS (LSH25 - Submitted February 4, 1991)

INVESTIGATOR: Thomas L. Hunt, M.D., Ph.D.
PharmacoDynamics Research, Inc.
Austin, Texas 78704

OBJECTIVES: To evaluate the PK and dose proportionality of zolpidem in healthy male adults following oral administration of single night-time doses of 2.5, 5.0, 10.0, 20.0 and 40.0 mg capsules.

FORMULATION:

	Lot number
2.5 mg capsule	GYG01-04A
5.0 mg capsule	DHV05-06A
10.0 mg capsule	KLZ05-03C
20.0 mg capsule	XCV05-02C
2 x 20.0 mg capsules	XCV05-02C

STUDY DESIGN:

This was a five-period, single-dose, randomized balanced Latin square design involving 45 subjects (39 Caucasians, 7 Hispanics, 1 Black, and 1 Asian - 3 drop out during the course of the study). A light meal was provided at 1700 hrs and the subjects received one of the above treatments at 2200 hrs. The fast continued 12 hrs following the dose. After a minimum 7-day washout period, subjects were crossed to the alternate treatment. Blood samples were obtained at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, and 12 hrs.

For the analysis of dose proportionality, the AUC values were normalized by dividing by the dose multiplier, i.e. dose/2.5. The normalized AUC values were then divided by the AUC for 2.5 mg and the 95% confidence interval for this ratio was calculated.

ASSAY:

The analytical determination of zolpidem concentrations in plasma samples was HPLC. The validation is as follows:

1. Sensitivity: The limit of quantitation (LOQ) was set at [redacted] ng/ml of zolpidem in plasma. The relative standard deviation (RSD) (N=6) of the peak height ratios was 8.3% and that of the measured concentrations from the nominal value was -0.2%. From the subject sample analyses, at the LOQ of [redacted] ng/ml the RSD for the back-calculated concentration was 13.4% with a deviation of 1.0% from the theoretical concentration.

2. Linearity: The calibration curves for zolpidem in plasma were linear in the concentration range from [redacted] ng/ml, with correlation coefficients greater than 0.9995. Calibration standards of [redacted] ng/ml were used. From the subject sample analyses, the relationship between peak height ratio and concentration for zolpidem was also linear in the curve ranges from [redacted] ng/ml, with correlation coefficients which exceeded 0.9958.

3. % Accuracy: Data from the methods validation report document all of the daily mean (N=6) and overall mean (N=18) values were within 4% of their expected values. In the analytical report of subject sample analyses the method accuracy was determined by comparing the means of the measured concentrations with the nominal concentrations of zolpidem in fortified plasma. For zolpidem, the deviations of the mean values from theoretical concentrations were -4.3% for [redacted] ng/ml quality control samples and 0.7% for the quality control sample [redacted] ng/ml.

4. Precision: From the methods validation report, the within-day precision of the method was determined from the relative standard deviation (RSD) of 6 replicate analyses of each of the 3 control pools. The overall precision of the method was determined from the RSD of 18 analyses of the 3 control pools over 3 days. The within-day precision ranged from 0.9% to 2.7% RSD (N=6) for zolpidem at all 3 quality control levels. The overall precision was 2.3%, 1.9% and 1.1% RSD (N=18) for the 3, 30 and 300 ng/ml zolpidem controls, respectively. From the subject sample analytical report the variability of the back-calculated concentrations of the calibration standards ranged from 2.3% to 13.4% for zolpidem. The between-day precision was determined at levels of 3, 30, and 300 ng/ml in replicate analyses (n=99, n=114 and n=107, respectively). The between-day variability did not exceed 6.8%.

5. Specificity: In the methods validation report, specificity was assessed from seven plasma pools tested for endogenous interferences. No interfering peaks were found at the retention times of zolpidem or the internal standard for the pools tested.

The assay is acceptable.

RESULTS:

The following tables show the mean results of the study. Individual subject data is found in Volume 2.

TABLE. The mean (%CV) zolpidem PK parameters of 2.5, 5, 10, 20, and 2x20 mg capsules.^(ng.h/ml), ^^(ng/ml),*(hrs)

DOSE (mg)	2.5	5	10	20	40
AUC^(0-12)	131.4	259.8	513.9	1004.2	1981.5
%CV	48	46	45	48	44
Range					
AUC^(inf)	144.3	281.6	551.5	1100.4	2158.6
%CV	58	52	50	55	51
Range					
Cmax^^	30.0	58.6	120.8	220.5	388.8
%CV	39	37	39	40	33
Range					
tmax (hrs)	1.61	1.56	1.52	1.70	2.43
half-life*	2.72	2.64	2.53	2.59	2.54
Range					

TABLE. The mean normalized values and the 95% confidence intervals and Ratios (N=42*).

					95% C.I. and Ratio		
	2.5	5	10	20	5/2.5	10/2.5	20/2.5
AUC[0-12]	131.4	128.6	128.5	125.2	0.979	0.978	0.975
					0.91-1.05	0.91-1.05	0.90-1.05
AUC[INF]	144.3	139.3	137.9	140.4	0.966	0.956	0.973
					0.89-1.05	0.88-1.05	0.90-1.06
C_{max}	29.9	29.1	30.2	28.0	0.972	1.008	0.934
					0.88-1.07	0.92-1.11	0.84-1.05
T_{max}(hr)	1.6	1.6	1.5	1.7	0.963	0.944	1.070
					0.79-1.15	0.74-1.18	0.83-1.37
T1/2(hr)	2.72	2.63	2.53	2.61	0.965	0.928	0.957
					0.90-1.04	0.86-1.00	0.90-1.01

*Notes: Subjects 7 and 44 have no data for zolpidem 2.5 mg and subjects 48, 50, and 55 were replacement subjects. These subjects were excluded from analysis.

Table. The mean dose proportionality assessment between 2.5 mg and 2x20 mg (N=40**).

Parameter	2.5 mg	40 mg	95% C.I. and Ratio 40 mg/2.5 mg
AUC [0-12] (ng.hr/ml)	132.51	125.23	0.945 0.867-1.036
AUC [0-INF] (ng.hr/ml)	145.92	137.21	0.940 0.860-1.039
C_{max} (ng/ml)	30.02	24.53	0.817 0.729-0.920
T_{max} (hour)	1.61	2.45	1.519 1.205-1.878
T 1/2 (hour)	2.75	2.57	0.935 0.855-1.028

** Notes: Ratios and confidence intervals for the 40 mg dose are based on data from the same 40 subjects from the 2.5 mg group.

COMMENT:

1. It can be concluded that the extent of absorption is linear and proportional over the dosing range as assessed by the analysis of AUC and the 95% confidence intervals for normalized ratios.

CONCLUSION:

The recommended dosing range in the labeling is 5 mg, 10 mg, 15 mg, and 20 mg. The results of this study can be used to support dose proportionality.

TITLE: A MASS BALANCE STUDY OF THE ELIMINATION OF RADIOACTIVITY FOLLOWING ORAL ADMINISTRATION OF 20 MG OF C-14 ZOLPIDEM TO HEALTHY VOLUNTEERS (STUDY IGB01).

DESIGN:

This study was design to determine the routes of elimination of zolpidem through mass balance and to identify metabolites. Radiolabelled zolpidem was administered orally as a single 20.24 mg encapsulated powder to 3 healthy male volunteers. The following samples were collected: Urine was collected at 0-3, 3-6, 6-9, 12-24 hr intervals and then daily up to 120 hrs after administration. Feces were collected daily for 5 days. Blood samples were obtained at 0, 1, 2, 3, 4, 5, 6, 8, 10, 24, 33, 48, 56, 72, and 96 hrs after administration.

ANALYTICAL METHODOLOGY:

Plasma and urine samples were analyzed by measurement of C-14 radioactivity. The correction for quenching was determined by means of a calibration curve. The counting efficiency was 75% and the background radioactivity was 16 dpm. Fecal samples were homogenized and then burned before measure of C-14 radioactivity. The concentration of zolpidem in the plasma or urine was measured by HPLC method following a single extraction by diethyl ether. Plasma, urine, and fecal samples were analyzed to identify metabolites of zolpidem which were separated by HPLC and identified by GC-MS.

RESULTS:

Table. Urinary and fecal excretion of radioactivity in 3 subjects 120 hrs after a single oral dose of C-14 zolpidem expressed as % of the dose of radioactivity administered.

Subject	1	2	3
Urine(%)			
Feces(%)			
Total			

COMMENT:

1. The majority of zolpidem and metabolites are eliminated via renal excretion. SL 84.0589 is the major metabolic product in the urine. The aromatic hydroxylation metabolites are present only in feces. The identified metabolites account for 85% of the radioactivity recovered. The only circulating plasma metabolite occurring in detectable quantities is SL 84.0589 which is inactive.

2. The peak plasma concentration of total radioactivity was obtained in less than 1 hr. The plasma radioactivity decreased in a biphasic manner with a terminal half-life of 5.3 to 10.9 hrs which may due to metabolites; however, metabolite accumulation is not expected with once-a-day dosing.

C. SPECIAL POPULATION STUDIES:

TITLE: PHARMACOKINETICS OF ZOLPIDEM IN ELDERLY SUBJECTS (STUDY IFR25)

OBJECTIVE: To compare elderly to young PK results.

FORMULATION: 20 mg capsule LP 12209 [Not to-be-marketed]

DESIGN:

This was an open study involving 8 elderly subjects (5 female and 3 males; ages 70-85). The subjects were in satisfactory condition with no concomitant drug use prior to and during the study. A single 20 mg zolpidem capsule was administered. Blood samples were obtained at 0, 0.5, 1, 1.5, 2, 4, 6, 8, 10, 24, and 27 hrs. The PK parameters in the elderly were compared to young adults (age 20-40 years) obtained in a prior study. Statistical analysis was by Student's t-test.

RESULTS:

The individual plasma concentrations and pharmacokinetic parameters are found Volume 1.42.

Table. The comparison of the mean PK parameters in elderly adults (N=8) to younger adults (N=34).

Age group	tmax hr	Cmax ng/ml	half-life hr	AUC ng hr/ml
20-40 (N=34)	1.44	255	2.2	955
%CV	89	55	26	77
70-85 (N=8)	1.80	384	2.9	1562
%CV	78	50	19	50

COMMENT:

1. After a single 20 mg dose, mean Cmax, half-life, and AUC values were 50%, 32%, and 64% increased in the elderly when compared to younger adults. Statistical analysis by Student's t-test indicated a significant difference between age groups for Cmax, half-life, tmax, and AUC.

CONCLUSION:

The results demonstrate a definite age related effect on the kinetics of zolpidem.

TITLE: ZOLPIDEM: ASSESSMENT OF SAFETY, PHARMACOKINETICS AND SLEEP FOLLOWING THE ADMINISTRATION OF REPEATED DOSES TO ELDERLY SUBJECTS (STUDY IFR38)

FORMULATION: 10 mg tablet [to-be-marketed] LP 12456-E

DESIGN:

This was a multiple dose study involving 11 volunteers (5 males and 6 females; ages 60-74). A 10 mg tablet of zolpidem was administered qd for 7 nights. Blood samples were obtained on day 1 after a single dose and on day 7 after seven doses at 0, 0.5, 1, 2, 4, 6, and 9 hours following drug administration. The following PK parameters were determined: Cmax, tmax, half-life, and AUC(inf) after the single dose on day 1 and after repeated administration on day 7. The data was analyzed by Student's t-test.

RESULTS:

The individual plasma concentrations and PK parameters following single dose and multiple dose administration are found in Volume 1.42.

Table. The mean (%CV) PK parameters of 10 mg zolpidem after single (day 1) and multiple dose administration (day 7) in elderly subjects.

	Day 1	Day 7
Cmax (ng/ml)	108 (42)	129 (59)
AUC(inf)	715 (51)	618 (54)
tmax (hr)	2.2 (47)	1.7 (81)
half-life (hr)	3.3 (31)	2.9 (35)

COMMENT:

1. By paired t-test, there was no significant difference between single dose PK parameters and multiple dose PK parameters (half-life, Cmax, and AUC) on days 1 and 7. After seven days of drug administration, zolpidem did not accumulate as determined by Cmax and AUC ratios. This is to be expected because of the short half-life of zolpidem and qd dosing.

TITLE: PHARMACOKINETICS OF ZOLPIDEM IN THE ELDERLY SUBJECT (IV VS ORAL) (STUDY IFR34)

OBJECTIVE: To compare zolpidem PK parameters in elderly subjects to younger subjects after a single oral dose or iv infusion.

DESIGN:

This was an open, two-way crossover study involving 9 subjects (7 females, 2 males; ages 81-95). Period 1 consisted of a single 10 mg zolpidem capsule [Not to-be-marketed] administered after an overnight fast with 150 ml of water. Period 2 consisted of a 20 min intravenous infusion (1 mg/ml; rate of 0.5 mg/min) of zolpidem. After a 7 day washout, subjects were crossed to the alternate formulation. Blood samples were obtained at the following times:
oral: 0, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, and 30 hours
iv: 0, 0.33, 0.66, 1, 2, 3, 4, 6, 8, 12, 24, and 30 hours.

The following PK parameters were calculated: Cmax, tmax, half-life, AUC, Vd, clearance, and absolute bioavailability. The results were compared to PK parameters obtained from a younger age group from an earlier study (age 19-31, 10 females and 12 males). A one-way ANOVA was used to compared all parameters.

RESULTS:

The individual plasma concentrations and pharmacokinetic parameters are found in Volume 1.42.

Table. The mean (%CV) PK parameters in elderly (N=9) and young subjects (N=20) following oral administration of 10 mg zolpidem capsule.

	ELDERLY	YOUNG
Cmax (ng/ml)	238 (44)	138 (38)
AUC(0-T) (ng*hr/ml)	1064 (41)	362 (62)
half-life (hr)	2.5 (28)	1.5 (30)
F	53 (51)	67 (30)

Table. The mean (%CV) PK parameters in elderly and young subjects following zolpidem iv administration.

	Cend.inf ng/ml	AUC ng hr/ml	half-life hr	Cl L/hr/kg	Vd L/kg
Elderly	1906 (86)	2178 (36)	2.5 (33)	0.09 (35)	0.34 (47)
Young	196 (22)	483 (53)	1.7 (26)	0.26 (52)	0.54 (16)

COMMENT:

1. Consistent with the previous elderly to young comparison study is a significant difference in the PK parameters of zolpidem between the elderly and the young following both oral and iv routes of administration. The systemic bioavailability of a 20 mg oral dose of zolpidem was decreased approximately 20%, total body clearance decreased significantly from 0.26 L/hr/kg in the young to 0.09 L/hr/kg in the elderly (65% decrease), and AUC was approximately 3-fold greater in the elderly. In spite of the decrease systemic bioavailability seen in the elderly, the decrease in the clearance of zolpidem probably accounts for the higher levels and longer half-life. The PK results demonstrate a definite age related effect on the kinetics of zolpidem and suggest the need to consider the age of the patient when dosing elderly patients.

CONCLUSION OF THE 3 ELDERLY STUDIES:

The sponsor recommends in the labeling that the initial dose for elderly be 5 mg with the total dose not to exceed 10 mg. Based upon the kinetics results of these studies, the statement appears to be justified; however, the reviewing medical officer is asked to consider the clinical consequences of the PK differences and assess the validity of this statement.

TITLE: NOCTURNAL PHARMACOKINETICS OF ZOLPIDEM IN CHILDREN (STUDY IFR44)

DESIGN:

This was a single-dose study involving six children (5 boys and 1 girl, ages 6 to 14). A 10 mg capsule [Not to-be-marketed] was administered with a 100 ml of water an hour to a half-hour after a meal. Blood samples were obtained at 0, 20, 40, 60, 80, 100 min, 2, 3, 4, 6, 8, and 10 hrs after administration.

RESULTS:

The individual data is found in Volume 1.42.

Table. The mean pharmacokinetic parameters of zolpidem in children after a 10 mg capsule.

Cmax ng/ml	AUC(inf) ng/ml*hr	tmax hr	half-life hr	Cl/F L/kg/hr
142 (50%)	326 (47%)	1.3 (75%)	2.0 (37%)	0.86 (28%)

COMMENT:

Estimated clearance values ranged from 0.64 to 1.18 L/h/kg which is 2-3 times higher than clearance values determined in adults. There was no direct comparison with adults performed. However, the PK parameters of Cmax, AUC, and half-life are decreased when compared to adults. The results indicate an age related difference in the kinetics of zolpidem.

CONCLUSION:

A comment concerning the administration of zolpidem in children is not under the Dosage and Administration section in the proposed labeling. It is not known if the sponsor intends to recommend this product for administration in children. However, the results of this study can be used to support information in labeling if zolpidem is to be recommended for use in children.

TITLE: ZOLPIDEM AND CHRONIC HEPATIC INSUFFICIENCY (STUDY IFR20)

DESIGN: This was an open trial involving 8 patients with clinical manifestations of compensated hepatic cirrhosis and 8 healthy subjects who received a single 20 mg oral dose of zolpidem.

RESULTS:

The individual data are found in Volume 1.44 starting with page 044-0020.

Table. A comparison of the mean (%CV) PK parameters of 20 mg zolpidem in patients with hepatic insufficiency (N=8) to healthy subjects (N=8).

	Hepatic	Healthy	Outcome
Cmax (ng/ml)	498 (77%)	250 (22%)	p<0.01
tmax (h)	0.7 (77%)	0.7 (57%)	NS
AUC (inf)	4203 (90%)	788 (35%)	p<0.05
half-life a (hr)	1.4 (43%)	x	
half-life b (hr)	9.9 (76%)	2.2 (12%)	p<0.05

a half-life - distribution half-life of the drug
b half-life - elimination half-life

COMMENT:

1. Following a single 20 mg oral dose to patients with cirrhosis, blood levels in liver patients were higher than those obtained in healthy subjects could be followed for up to 27 hrs in cirrhotic patients. The blood levels from hepatic patients were model according to a 2-compartment model, and it was found there were significant increases in AUC from 788 to 4203 ng*ml/hr (approximately a 5 fold increase), Cmax from 250 to 498 ng/ml (2 fold increase), and elimination half-life from 2.2 hrs in normal subjects to approximately 10 hrs in hepatic patients. Since the primary route of zolpidem elimination is hepatic metabolism, the results of this comparison are to be expected.

CONCLUSION:

The results of this study indicate there is a very significant effect of liver disease on the elimination and thus the kinetics of zolpidem and that dose adjustment is warranted. The results of this are taken into account under the Dosage and Administration section of the package insert in which the sponsor recommends a 5 mg initial dose, not to exceed 10 mg in such patients. Based upon the kinetics results of this study, the statement appears to be justified; however, the reviewing medical officer is asked to consider the clinical consequences of the PK differences.

TITLE: STUDY OF THE PHARMACOKINETICS OF ZOLPIDEM IN PATIENTS WITH RENAL FAILURE (STUDY IFR12)

OBJECTIVES:

To determine whether renal failure interferes with the PK of zolpidem and to insure that zolpidem was eliminated by hemodialysis.

DESIGN:

This was an open trial involving 2 groups as follows who were administered a 10 mg zolpidem iv infusion over 20 min:

I. Dialysis Patients
   Ia. 8 patients treated by hemodialysis received an injection of zolpidem in order to evaluate the dialysance of this drug (creatinine clearance between 0 and 8 ml/min). The drug was administered 3 hr before dialysis.
   Ib. 8 patients received the drug in order to study the PK of zolpidem between 2 dialysis sessions (creatinine clearance between 0 and 5 ml/min.
II. 8 patients with stable chronic renal failure not requiring dialysis received the drug to study the PK of the compound after a single dose (creatinine clearance 5.71 to 47 ml/min)

RESULTS:

Table. A comparison of mean (%CV) PK parameters of zolpidem between renal failure (Group Ib and II, N=16) and healthy subjects (N=20).

	Cendinf (ng/ml)	half-life (hr)	AUC (inf) (ng.hr/ml)	Cl (L/h)	Vd (L/kg)
Renal failure	228 (38)	2.8 (57)	708 (80)	0.38 (115)	0.91 (40)
Healthy subjects	197 (22)	1.7 (26)	483 (52)	0.26 (52)	0.54 (16)
Outcome	NS	NS	NS	NS	$p<0.05$

COMMENTS:

1. The results of this study followed iv administration and not an oral dose. Statistically, it can be concluded that impaired renal function had no significant influence on the PK parameters of zolpidem when compared to healthy subjects except for a significant difference in the volume of distribution. In renal patients, the amount of zolpidem excreted unchanged over 10 hrs expressed as a percent of dose was 0.16% (38% CV). There was an increase in half-

life from 1.7 to 2.8 hrs and a 46% increase in AUC from 483 to 708. From the dialysis patients, the dialysis of zolpidem was virtually nil.

2. The results presented in this study are following intravenous administration rather than a tablet. A definite conclusion regarding the lack of renal disease on the pharmacokinetics of zolpidem following an oral dose cannot be made. A study in renal disease patients in which a tablet is administered is suggested as a Phase IV study.

TITLE: PHARMACOKINETICS OF ZOLPIDEM IN OBESE PATIENTS (STUDY IFR43)

DESIGN:

This was an open, 2 period crossover study involving 20 subjects (10 females and 10 males) who were over their ideal body weight as follows:
IBW (women) = 45 kg ± 0.9 kg/cm above or below 152 cm
IBW (men) = 50 kg ± 0.9 kg/cm above or below 152 cm

In period 1 subjects were administered a 10 mg oral tablet following overnight fasting and in period 2 a 10 mg 15 min infusion. There was a 2 day washout between periods. The results were compared to PK parameters of a 10 mg oral tablet in lean subjects obtained in a prior study (IGB09).

RESULTS:

Table. The mean (%CV) PK parameters in 20 obese subjects compared to lean subjects following a 10 mg oral tablet.

	tmax (hr)	Cmax (ng/ml)	Half-life (hour)	AUC (ng.h/ml)	F (%)	Vd (L/kg)	Cl/F (L/h/kg)
Obese	2.4	74.2	2.7	424	[illegible]	0.95	0.28
%CV	37	48	50	72	40	37	48
Lean	1.2	143	1.7	453	68	0.54	0.26
%CV	74	55	26	81	36	16	52

Table. The mean (%CV) PK parameters following a 10 mg iv infusion in obese patients.

Cendinf (hr)	Cl (L/h/kg)	Half-life (hour)	AUC (ng.h/ml)	Vd (L/kg)
162.3	0.278	2.6	343	0.85
36	55	68	44	37

COMMENTS:

1. In the obese patients, the mean Cmax and AUC values were 48% and 6% decreased compared to lean subjects, respectively. The mean half-life and volume of distribution increased 50% and 57% respectively in the obese compared to the lean group with both groups having similar total body clearance for zolpidem. It is not known if this kinetic difference would have any significant impact on the effectiveness of the drug. The Reviewing Medical Officer is asked to consider whether a dosage adjustment upward for obese patients is warranted.

EFFECT OF GENDER

A study to determine the effect of gender on zolpidem PK was submitted; however, background and study design was not included. Subjects were healthy males and females (age: 19-45).

RESULTS:

Table. The mean PK parameters of 20 mg zolpidem.

	N	Cmax (ng/ml)	AUC (ng/ml*hr)	tmax (hr)	half-life (hr)
Females	16	340	1264	1.1	2.7
Males	49	234	859	2.0	2.3

COMMENT:

Both Cmax and AUC were approximately 45% higher in females than males with tmax occurring 1 hour sooner in females. The results suggest a gender related difference; however, the lack of specific details such as study design and individual data make it difficult to draw a definite conclusion.

D. ZOLPIDEM-DRUG INTERACTIONS STUDIES

The results of zolpidem-drug interaction studies are found in Volumes 1.45, 1.46, and 1.47.

TITLE: STUDY OF THE POSSIBLE INTERACTION BETWEEN ZOLPIDEM AND IMIPRAMINE

DESIGN:

This was a 3 way crossover study involving 6 healthy subjects who were administered the following tx after an overnight fast: 20 mg zolpidem capsule, 75 mg imipramine, and 20 mg zolpidem + 75 mg imipramine.

RESULTS:

Table. The mean (%CV) PK parameters of zolpidem.

	tmax (hr)	Cmax (ng/ml)	half-life (hr)	AUC (inf) (ng.h/ml)
Zolpidem	1.0 (49)	257 (61)	2.0 (37)	1103 (76)
Zolpidem + Imipramine	2.0 (86)	296 (55)	1.8 (27)	1159 (44)

Table. The mean (%CV) PK parameters of imipramine.

	tmax (hr)	Cmax (ng/ml)	AUC (inf) (ng.h/ml)	half-life hr
Imipramine	1.7 (29)	49. (32)	773 (44)	9.3 (18)
Zolpidem + Imipramine	3.5 (84)	41.3 (35)	942 (70)	10.6 (39)
Outcome	NS	S	NS	NS

Table. The mean (%CV) PK parameters of desipramine.

	tmax (hr)	Cmax (ng/ml)	AUC (inf) (ng.h/ml)
Imipramine	11.8 (87)	11.3 (35)	179 (31)
Zolpidem + Imipramine	13.8 (67)	11.0 (44)	217 (40)

COMMENT:

1. By ANOVA, zolpidem alone and in combination with imipramine and desipramine showed no significant drug-drug interaction ($p > 0.05$) on the PK of zolpidem. There was slight effect on the Cmax of imipramine but no effect on its metabolite desimipramine.

TITLE: STUDY OF THE POSSIBLE INTERACTION BETWEEN ZOLPIDEM AND ALCOHOL

DESIGN:

This was a 2 way crossover study involving 12 healthy subjects who were administered 20 mg zolpidem tablet and 0.6 ml of alcohol per kg of body weight.

Blood samples were collected at 2, 3, 4, and 6 hrs which precludes a comparison of PK parameters; however the blood levels of zolpidem with and without alcohol were compared and the results showed no significant effect of alcohol on the blood levels of zolpidem for those hrs.

TITLE: EVALUATION OF FLUMAZENIL AS AN ANTAGONIST OF ZOLPIDEM

DESIGN:

This was a randomized study involving 9 healthy subjects who were administered 10 mg zolpidem injection over 1 min followed 17 min later by a second injection of 1 mg flumazenil infused over 1 min.

RESULTS:

Table. The mean (%CV) PK parameters of zolpidem alone and with flumazenil.

	half-life (hr)	AUC (inf) (ng.h/ml)
Zolpidem + Flumazenil	1.23 (33%)	570 (42%)
Zolpidem	1.61 (53%)	801 (90%)
Outcome	NS	NS

COMMENTS:

1. After zolpidem iv administration, the elimination half-life varied from 0.71 to 3.22 hr. After administration with flumazenil, it varied from 0.52 to 1.69 hrs. These values were found not to be significantly different by ANOVA.

2. The AUC values for zolpidem varied from 249 to 2218 ng.h/ml while with flumazenil varied from 224 to 966 ng.h/ml. There was no significant difference between treatments even though a trend towards smaller AUC values after zolpidem with flumazenil seems present.

TITLE: STUDY OF INTERACTION BETWEEN ZOLPIDEM AND CHLORPROMAZINE (STUDY IBE03)

DESIGN:

This was a 2-way crossover study involving 6 subjects (3 men and 3 women) who were administered 20 mg zolpidem capsule alone and 20 mg zolpidem capsule plus 50 mg chlorpromazine after an overnight fast.

RESULTS:

Table. The mean PK parameters (%CV).

	tmax (hr)	Cmax (ng/ml)	half-life (hr)	AUC (inf) (ng.h/ml)
Zolpidem	0.75	324	1.7	812
%CV	33	45	43	51
Zolpidem + Chlorpromazine	1.30	286	2.1	967
%CV	75	66	35	58
Comparison	NS	NS	NS	NS

COMMENT:

1. A 50 mg chlorpromazine dose is a low dose. By ANOVA, the results showed no significant drug-drug interaction ($p > 0.05$) on the PK parameters of zolpidem.

2. The effect on chlorpromazine were not determined due to assay limitations.

TITLE: STUDY OF INTERACTION BETWEEN ZOLPIDEM AND HALOPERIDOL (STUDY IFR21)

DESIGN:

This was a 2-way crossover study involving 6 subjects (3 men and 3 women) who were administered 20 mg zolpidem capsule alone and 20 mg zolpidem plus 2 mg haloperidol after an overnight fast.

RESULTS:

Table. The mean PK parameters (%CV).

	tmax (hr)	Cmax (ng/ml)	half-life (hr)	AUC (inf) (ng.h/ml)
Zolpidem	1.2	226	2.4	733
%CV	61	48	31	47
Zolpidem + Haloperidol	0.75	221	2.0	597
%CV	33	33	24	36
Comparison	NS	NS	NS	NS

COMMENT:

1. By two-way ANOVA, the results showed no significant drug-drug interaction ($p > 0.05$) on the PK parameters of zolpidem.

2. Effects on haloperidol could not be measured due to assay limitations.

TITLE: STUDY OF POSSIBLE INTERACTION BETWEEN ZOLPIDEM AND CIMETIDINE AND RANITIDINE

INVESTIGATOR: C. Harvengt, Brussels, Belgium

DESIGN:

This was an open two-period crossover study involving 3 healthy male and 3 healthy female volunteers. This study comprised 2 products sequences separated by an interval of 20 days. Each sequence comprised the administration of the following treatments:

Period I: Days 1, 5, 21 - 20 mg zolpidem
Days 4-23 - 200 mg tid and 400 mg hs (1000 mg) cimetidine

Period II: Days 1, 5, 21 - 20 mg zolpidem
Days 4-23 - 150 mg bid (300 mg) ranitidine

Zolpidem was administered only once before treatment with one or the other H2 product.

RESULTS:

Table. The mean (SEM) zolpidem PK parameters. S1 - Zolpidem alone, S2 - after 1 day of cimetidine, S3 - after chronic cimetidine, S4 - after 1 day of ranitidine, S5 - after chronic ranitidine

	tmax (hr)	Cmax (ng/ml)	half-life (hours)	AUC (0-inf) (ng.h/ml)
S1	0.6 ± 0.08	429 ± 34	1.9 ± 0.3	1082 ± 152
S2	0.8 ± 0.11	474 ± 50	2.1 ± 0.3	1411 ± 278
S3	0.9 ± 0.24	336 ± 69	2.6 ± 0.7	1250 ± 237
S4	0.8 ± 0.11	387 ± 49	1.5 ± 0.2	1076 ± 165
S5	1.2 ± 0.38	351 ± 40	1.7 ± 0.3	1014 ± 152

COMMENT:

1. Only the effect of the H_2 blockers on zolpidem was tested. Based on ANOVA, the PK parameters of AUC, Cmax, tmax, and half-life of zolpidem following both single dose and multiple doses of cimetidine and ranitidine were not affected.

CONCLUSION:

The results of this study can be used to support the statement in the labeling.

IV. DISSOLUTION

METHOD:

USP Apparatus 2 (paddle) method at 50 RPM with 900 ml of water, phosphate buffer (pH 8), and 0.01 N HCl (pH 2) at 37°C. A sample was removed at 5, 10, 15, and 30 min times. The Lots 9060.1 and PT-232-90 are 5 mg tablets and Lots 9075.1 and PT-233-90 are 10 mg tablets used in Studies LSH27 and LSH91 were manufactured according to the current formulation and were from production size batches. One batch (5 mg, Lot 8035) is of the formulation contained in the original NDA. The results are attached.

RESULTS:

TABLE. The range of %dissolution of zolpidem tablet in water.

	5 min	10 min	15 min	30 min
Batch 8035 (5 mg)				

TABLE. The range of %dissolution in 0.01 N HCl (pH 2).

	5 min	10 min	15 min	30 min
Batch 8035 (5 mg)				
Batch 9069 (5 mg)				
Batch PT-232-90				
Batch 9075 (10 mg)				
Batch PT-233-90				

TABLE. The range of %dissolution in phosphate buffer (pH 8).

	5 min	10 min	15 min	30 min
Batch 8035 (5 mg)				

COMMENTS:

1. The tablet is a film coated tablet which may account for the large degree of variability seen in the percent dissolution in the first 5 minutes. However, both 5 and 10 mg tablets are greater than [redacted]

CONCLUSION:

Based on this information a specification of NLT [redacted] can be set.

CONFIDENTIAL

DISSOLUTION TEST : WATER

STILNOX
Stilnox scored film coated tablet 5mg

Batch : 8035

TIME (minute)	5	10	15	20	25	30
sample 1						
sample 2						
sample 3						
sample 4						
sample 5						
sample 6						
average	37,11	98,95	100	99,65	101,0	99,83
S.D	8,920	1,204	1,468	1,517	3,750	1,495
RSD %	24,03	1,217	1,468	1,522	3,713	1,497

CONFIDENTIAL

DISSOLUTION TEST : HCL 0,01N

STILNOX
Stilnox scored film coated tablet 5mg

Batch : 9035

TIME (minute)	5	10	15	20	25	30
sample 1						
sample 2						
sample 3						
sample 4						
sample 5						
sample 6						
average	56.38	101.7	102,3	101.8	102,0	102,1
S.D	8,314	2.165	1,540	1,603	1,731	1,807
RSD %	14,74	2,132	1.505	1,574	1,697	1,769

CONFIDENTIAL

DISSOLUTION TEST : pH = 8.0

STILNOX
Stilnox scored film coated tablet 5mg

Batch : 8035

TIME (minute)	5	10	15	20	25	30
sample 1						
sample 2						
sample 3						
sample 4						
sample 5						
sample 6						
overage	50,55	93,23	98.73	102,3	101,5	102,3
S.D	5,675	2,823	2,087	5,009	1,859	2,057
RSD %	11,23	3,028	2,114	4,894	1,831	2,010

LSH91

5 MG TABLET DISSOLUTION PROFILE

SAMPLE NO.	5 MIN. % DISSOL.	10 MIN. % DISSOL.	15 MIN. % DISSOL.	30 MIN. % DISSOL.
#.1				
#.2				
#.3				
#.4				
#.5				
#.6				
#.7				
#.8				
#.9				
#.10				
#.11				
#.12				
g. of 12	75.1	90.2	95.2	97.3
nge				
d. Dev.	8.1	3.9	2.5	1.5

LSH91

10 MG TABLET DISSOLUTION PROFILE

SAMPLE NO.	5 MIN. % DISSOL.	10 MIN. % DISSOL.	15 MIN. % DISSOL.	30 MIN. % DISSOL.
NO. #.1				
NO. #.2				
NO. #.3				
NO. #.4				
NO. #.5				
NO. #.6				
NO. #.7				
NO. #.8				
NO. #.9				
NO. #.10				
NO. #.11				
NO. #.12				
Avg. of 12	71.9	93.7	97.3	98.9
Range				
Std. Dev.	7.4	4.9	3.5	2.9

LSH 27

DISSOLUTION TEST - 0,01 N HCL

STILNOX
Film coated tablets 5 mg

Batch : 9059.1

TIME (minute)	5	10	15	20	25	30
sample 1						
sample 2						
sample 3						
sample 4						
sample 5						
sample 6						
sample 7						
sample 8						
sample 9						
sample 10						
sample 11						
sample 12						
average	55,27	100,9	101,7	101,4	101,4	101,8
S.D	27,59	3,108	3,283	2,895	3,023	3,975
RSD %	49,92	3,080	3,225	2,854	2,981	3,905

-SH127

DISSOLUTION TEST

STILNOX
Film coated tablets 10 mg

Batch : 9075.1

TIME (minute)	5	10	15	20	25	30
sample 1						
sample 2						
sample 3						
sample 4						
sample 5						
sample 6						
sample 7						
sample 8						
sample 9						
sample 10						
sample 11						
sample 12						
average	50,65	98,06	98,55	98,51	98,58	98,65
S.D	22,51	2,808	2,689	2,726	2,809	2,735
RSD %	44,44	2,863	2,728	2,767	2,849	2,772

V. SPECIAL STUDIES

A. PROTEIN BINDING STUDY GANANSIA/NAp v38

The binding of zolpidem to plasma protein was determined by *in vitro* equilibrium dialysis at 37° C and *in vivo* by chronic administration to determine parent drug/metabolite interaction.

For *in vitro*, increasing concentrations of ^{14}C-zolpidem were tested from 40 to 790 ng/ml. The results indicate that 92.5% was bound to plasma protein and remain constant with increasing drug concentrations. It was further determined that zolpidem was bound 66% and 57% to albumin and acid glycoprotein respectively.

For drug interaction, salicylic acid, chlorpromazine, haloperidol, imipramine and desipramine did not affect zolpidem protein binding. After chronic *in vivo* treatment with zolpidem, protein binding was not modified indicating that the metabolites do not compete for binding with the parent drug.

B. ZOLPIDEM CLEARANCE IN BREAST MILK:

Following the oral administration of zolpidem to 5 mothers during lactation, the total amount of zolpidem excreted in milk were less than 0.02% of the administered dose. Breast milk clearance varied from 0.63 to 2.61 ml/hr. Zolpidem concentrations were no longer measurable in the 3-13 hrs sample. The milk/plasma ratio at 3 hrs after administration was 0.13 ± 0.01. The results demonstrate that zolpidem is excreted in human breast milk and is noted in the labeling on page 13.

VI. OVERALL COMMENTS:

1. Study LSH27 (filed February 4, 1991) demonstrated bioequivalency between the 10 mg clinical capsule and the 10 mg to-be-marketed tablet. Study LSH91 (filed June 28, 1991 and reviewed in an addendum review) demonstrated bioequivalency between 2x5 mg to-be-marketed tablets and 1x10 mg to-be-marketed tablets both from production size batches manufactured in the production facility.

2. Zolpidem is a highly variable drug as indicated by the large degree of intersubject variation seen for its pharmacokinetic parameters e.g. from Study LSH25 for the 10 mg dose, its AUC(0-12) ranged from 174 to 1121 and from Study IGB09 AUC(inf) values ranged from 93-1439 and Cmax values ranged from 45 to 346. Both tmax and half-life values were consistent between studies.

3. The absolute bioavailability of zolpidem was determined to be 67.5%, 66.6%, and 70.2% for the 10 mg capsule, 10 mg scored-tablet, and 20 mg tablet respectively. An extraction ratio of 0.19 was calculated for zolpidem.

4. Following multiple dose administration in normal healthy subjects, there was no significant accumulation of zolpidem as determined by mean Cmax and AUC ratios from Day 1 to Day 15 of drug administration. Antipyrine metabolism, a measure of liver function metabolism, was not significantly affected indicating that zolpidem did not induce liver metabolism following multiple dosing. However, inspection of individual subject data showed reduction as well as increases in the AUC and Cmax values of zolpidem on Day 15 following multiple dosing. It is not known if this reduction or increase seen after multiple dosing would indicate change in the effectiveness of the drug. The Medical Officer should evaluate if the effectiveness of the zolpidem is changing with time.

5. Zolpidem is metabolized through 3 metabolic pathways resulting in inactive metabolites: the major pathway is oxidation of the methyl group on the phenyl ring resulting in about 50% of the radioactivity eliminated in the urine and feces. The second pathway is oxidation of the methyl group attached to imidazopyridine moiety accounting for 11% of the dose. Hydroxylation of one to the aromatic rings represents 10% of the urinary and fecal excretion. Less than 1% of the drug is excreted unchanged in the urine. The urinary excretion of the metabolites is completed 120 hrs after sampling with 46-65% of the dose eliminated during the first 24 hours following administration. After 120 hours of sampling, 48-66% of the administered dose was found to be eliminated in the urine. After 5 days of fecal collection, 29-42% of the administered dose was found to be eliminated in the feces.

6. In elderly subjects, after a single dose there was an increase in Cmax, AUC and half-life by approximately 50%, 64%, and 32%

respectively when compared to younger adults. Based upon the kinetics results of this study, the statement concerning the dose adjustment in the elderly appears to be justified; however, the reviewing medical officer is asked to consider the clinical consequences of the PK differences.

7. Comparing Day 1 to Day 7 kinetic parameters following multiple dosing in elderly subjects, there was no significant change in kinetic parameters.

8. In children, zolpidem has a clearance rate that is 2-3 times faster than the clearance of 0.26 L/h/kg determined for adults. All other parameters are comparable.

9. There was significant differences between cirrhotic and healthy groups for Cmax, AUC and half-life values. The zolpidem Cmax and AUC were 2 and 5 times higher respectively in the hepatic disease patients compared to healthy subjects. Zolpidem is extensively metabolized with less than 0.2% of the dose excreted unchanged in the urine; therefore, its pharmacokinetics are sensitive to functional changes in the liver. Based upon the kinetics results of this study, the statement concerning dose adjustment in hepatic patients appears to be justified; however, the reviewing medical officer is asked to consider the clinical consequences of the PK differences.

10. A comparison of renally impaired patients to healthy subjects showed that only the volume of distribution was significantly modified in renal failure patients. The difference between the PK parameters of AUC, Cmax, and half-life was not significant. The results of the dialysis of zolpidem indicated that zolpidem was not removed by dialysis.

11. The interaction between zolpidem and imipramine, alcohol, flumazenil, chlorpromazine, haloperidol following single dose drug interaction studies was not significant.

12. Protein binding results for zolpidem indicate that it is approximately 92% bound to plasma protein which is not altered with increasing drug concentrations. There was no drug/drug protein binding interaction when zolpidem was tested with other drugs.

13. From the food effect study, there was a slight effect on the bioavailability of zolpidem when administered following a meal when compared to the fasted state.

VII. LABELING:

Under the Clinical Pharmacology section of the package insert, the following statements are something similar should be added:

1. For the description of various pharmacokinetic parameters in which the mean value is used, the sponsor should replace all ±SEM with coefficient of variation (%CV). This will give a clearer indication of the large degree of variability associated with this drug.

2. The following statement should be added to take into account the results of the food effect study.

> "From a food effect study comparing the administration of zolpidem following a meal and fasting, the AUC and Cmax values were significantly decreased 15% and 25% respectively, while tmax was found to be significantly increased from 1.4 to 2.2 hrs when zolpidem was administered 20 min after a meal. The half-life remained unchanged."

3. On page 10, the following should be added to that statement:

> "In single dose drug interaction studies in healthy volunteers....etc"

4. The following should be added following the drug interaction statement on page 11,

> "However, the lack of a drug interaction following single dose administration does not predict a lack following chronic administration."

5. On page 2, the statement "The half-life is slightly longer in females than in males." The observed half-lives should be added.

6. On page 2, the statement

> "In the therapeutic dose range, zolpidem demonstrates linear pharmacokinetics."

should be change in order to be specific to:

> "In the therapeutic dose range of 5, 10, 15, and 20 mg, zolpidem demonstrated linear pharmacokinetics."

7. On page 11, drug interaction studies between zolpidem and digoxin and warfarin were not submitted. Therefore, the statement in the labeling concerning the lack of a drug interaction between zolpidem and digoxin and zolpidem and warfarin should be removed until the study is reviewed unless there are data from clinical studies to support the statement.

8. On page 3, the following statement:

> "Zolpidem binds to albumin and acid alpha-glycoprotein. The extent of binding to these proteins was 66 and 57%, respectively."

should be deleted and replaced with the following:

> "The protein binding of zolpidem is 92%."

9. On page 9, the following should be added to the second paragraph concerning renal impairment:

> "The data available for an intravenous study in impaired renal function patients indicate that dose modifications appears to be unnecessary; however, the patient should be carefully monitored."

APPENDIX 1

INDIVIDUAL SUBJECT PHARMACOKINETICS

27 Pages

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APPENDIX G.2

DEMOGRAPHY AND PATIENT CHARACTERISTICS

LSH25

VOLUME 5 of 8

FEBRUARY 4, 1991 SUBMISSION

Demographic and Baseline Characteristics

LSW25

Investigator: HUNT

SUBJECT	SEX	AGE	RACE	WEIGHT (kg)	HEIGHT (cm)	HEART RATE SUPINE	HEART RATE STANDING	SYSTOLIC BP SUPINE	SYSTOLIC BP STANDING	DIASTOLIC BP SUPINE	DIASTOLIC BP STANDING
1	M	26	HISPANIC	67.1	170.0	44	48	100	110	62	70
2	M	21	CAUCASIAN	70.3	176.0	64	66	106	112	62	68
3	M	27	ASIAN	72.5	170.0	58	58	132	130	74	70
4	M	19	CAUCASIAN	55.0	170.0	64	72	106	112	60	74
5	M	23	CAUCASIAN	92.9	178.0	60	64	120	108	70	80
6	M	34	CAUCASIAN	73.0	178.0	68	80	120	130	82	84
7	M	23	CAUCASIAN	80.5	172.0	52	64	102	108	70	80
8	M	25	BLACK	93.5	182.0	62	64	130	132	80	82
9	M	24	HISPANIC	75.9	176.0	66	72	118	126	78	90
10	M	23	HISPANIC	70.9	170.0	68	70	116	118	68	76
11	M	25	CAUCASIAN	85.2	172.0	58	62	104	110	60	70
12	M	19	CAUCASIAN	80.9	182.0	64	66	112	118	76	84
13	M	31	CAUCASIAN	73.2	160.0	52	70	102	102	66	72
14	M	21	CAUCASIAN	74.8	168.0	64	78	108	120	78	70
15	M	19	CAUCASIAN	78.8	188.0	64	72	120	122	70	76
16	M	19	CAUCASIAN	80.0	182.0	72	84	124	136	74	82
17	M	34	CAUCASIAN	87.9	182.0	50	48	110	110	70	80
18	M	22	CAUCASIAN	67.5	172.0	66	74	114	116	70	72
19	M	29	CAUCASIAN	72.3	172.0	60	84	104	110	70	64

Demographic and Baseline Characteristics

L3825

Investigator: HUNT

SUBJECT	SEX	AGE	RACE	WEIGHT (kg)	HEIGHT (cm)	HEART RATE		SYSTOLIC BP		DIASTOLIC BP	
						SUPINE	STANDING	SUPINE	STANDING	SUPINE	STANDING
20	M	22	CAUCASIAN	69.3	172.0	60	64	108	112	74	78
21	M	19	HISPANIC	72.4	176.0	60	72	110	120	6[illegible]	84
22	M	24	HISPANIC	68.0	160.0	60	6[illegible]	106	110	70	72
23	M	22	CAUCASIAN	72.0	162.0	56	80	108	104	62	60
24	M	24	CAUCASIAN	65.9	172.0	54	62	108	110	70	74
25	M	33	CAUCASIAN	80.4	178.0	56	64	108	112	80	86
26	M	19	CAUCASIAN	70.9	174.0	66	64	108	108	74	78
27	M	30	CAUCASIAN	75.4	176.0	80	82	118	122	66	68
28	M	38	CAUCASIAN	79.1	180.0	68	70	110	120	66	64
29	M	31	CAUCASIAN	72.0	166.0	74	78	118	118	72	84
30	M	24	CAUCASIAN	61.2	172.0	66	68	120	120	70	80
31	M	32	CAUCASIAN	77.0	176.0	55	58	132	140	74	80
32	M	20	CAUCASIAN	80.6	178.0	46	54	116	122	74	74
33	M	22	CAUCASIAN	58.0	170.0	52	70	104	106	58	64
34	M	32	HISPANIC	73.0	168.0	64	68	120	118	74	76
35	M	19	CAUCASIAN	66.5	170.0	68	74	114	120	64	70
36	M	22	CAUCASIAN	72.3	168.0	54	74	122	122	80	82
37	M	25	CAUCASIAN	67.4	174.0	60	66	118	120	70	70
38	M	35	CAUCASIAN	72.1	172.0	68	68	122	124	70	82

Demographic and Baseline Characteristics

LSH25

Investigator: HUNT

						HEART RATE		SYSTOLIC BP		DIASTOLIC BP	
SUBJECT	SEX	AGE	RACE	WEIGHT (kg)	HEIGHT (cm)	SUPINE	STANDING	SUPINE	STANDING	SUPINE	STANDING
39	M	25	CAUCASIAN	59.1	168.0	56	56	120	120	76	80
40	M	22	CAUCASIAN	81.4	184.0	60	64	106	110	68	70
41	M	22	CAUCASIAN	77.2	178.0	60	62	110	112	74	82
42	M	20	CAUCASIAN	71.2	170.0	54	60	118	116	58	64
43	M	23	CAUCASIAN	80.4	182.0	58	64	130	134	70	70
44	M	30	CAUCASIAN	58.1	174.0	67	56	110	102	64	70
45	M	42	CAUCASIAN	89.3	178.0	46	48	102	114	60	60
48	M	18	CAUCASIAN	68.5	178.0	60	66	108	110	60	64
50	M	22	CAUCASIAN	78.0	182.0	58	78	110	108	72	76
55	M	22	HISPANIC	77.9	172.0	54	70	118	120	74	80

26 Pages

Redacted

ANNOTATED PROPOSED LABELING
AND PROPOSED CONTAINER LABELS

20 Pages

Redacted

TABLE 51

TABLE 2 Individual plasma concentrations of zolpidem after single oral administration of zolpidem (20 mg) in capsule form :

A : alone

B : in combination with 2 mg of haloperidol

A

SL 80.0750	Times						
Subjects	.500	1.000	2.000	4.000	6.000	8.000	10.000
1							
2							
3							
4							
5							
6							
Mean	153.8000	170.3333	122.5000	84.3000	43.1667	22.5000	14.6667
S.E.	71.7687	35.0758	17.6517	13.7568	11.5540	7.0357	5.3769

(Time unit = h, Concentration unit = $ng.ml^{-1}$)

B

SL 80.0750 + Haloperidol	Times						
Subjects	.500	1.000	2.000	4.000	6.000	8.000	10.000
1							
2							
3							
4							
5							
6							
Mean	191.1667	168.0000	103.0000	56.6667	20.3333	13.3333	9.3333
S.E.	39.7546	21.0000	17.7200	11.1375	4.4247	2.4721	2.9059

(Time unit = h, Concentration unit = $ng.ml^{-1}$)

TABLE 52

TABLE 3 Individual pharmacokinetic parameters of zolpidem after single oral administration of zolpidem alone (A) or combined with 2 mg of haloperidol (B).

Pharmacokinetic parameters (SL 80.0750)

Subjects	Cmax (ng.ml^{-1}) A	Cmax (ng.ml^{-1}) B	tmax (h) A	tmax (h) B	t½ (h) A	t½ (h) B	AUC$_{0-\infty}$ (ng.ml^{-1}.h) A	AUC$_{0-\infty}$ (ng.ml^{-1}.h) B
KOU								
NOB								
VIN								
SAR								
VIR								
XIB								
Mean	226.3	221.16	1.16	0.75	2.36	2.03	732.8	597.1
S.D.	107.1	72.58	0.68	0.27	0.62	0.41	346.45	214.4
S.E.M.	43.75	29.6	0.27	0.11	0.25	0.17	141.4	87.5
CV(%)	47.35	32.81	58.5	36.5	26.40	20.5	47.27	35.9

Im 3

047--0037

TABLE 47

Table 3 Individual plasma zolpidem concentrations obtained after a single oral administration of 20 mg zolpidem in capsule form:

A = zolpidem alone.

C = combined with 50 mg chlorpromazine.

(A)

[22 SEP 1986 12h12] Preclin . 73••CHLORPROMAZINE Page 1

Subjects	Times .500	1.000	2.000	3.000	4.000	6.000	8.000	10.000	24.000	[illegible]
1-1.A										
2-2.A										
3-3.A										
4-4.A										
5-5.A										
6-6.A										
Mean	214.6667	289.3333	147.5000	102.3000	67.0000	33.8000	40.4000	11.0400	4.3000	?.70
S.e	62.2581	60.9099	38.5523	24.9132	14.9293	7.9398	22.9739	4.2256	0.3000	?.70

(Dose unit=MG ,Time unit=H ,Concentration unit=NG/ML)

(C)

[21 SEP 1986 12h12] Preclin . 73••CHLORPROMAZINE Page 1

Subjects	Times .500	1.000	2.000	3.000	4.000	6.000	8.000	10.000	24.000
1-1.C									
2-2.C									
3-3.C									
4-4.C									
5-5.C									
6-6.C									
Mean	240.1667	215.2300	173.1667	132.0000	92.6667	64.2500	31.4000	15.0000	3.0000
S.e	83.1222	46.9933	33.5416	37.6294	26.0587	17.7466	7.0905	4.3520	0.0000

(Dose unit=MG ,Time unit=H ,Concentration unit=NG/ML)

TABLE 48

047--0038

Table 4 Individual serum chlorpromazine concentrations obtained after a single oral administration of 50 mg chlorpromazine in capsule form:

B = alone.

C = combined with 20 mg zolpidem.

(B)

(6 NOV 1984 17h84) Problem : SL800750/CHLORPROMAZ Page 1

Subjects	.500	1.000	2.000	3.000	4.000	6.000	8.000	10.000	24.000	27.000	32.000
1-1.B											
2-2.B											
3-3.B											
4-4.B											
5-5.B											
6-6.B											
Mean	1.5933	10.0780	8.3733	9.0180	7.2501	3.8733	2.7917	2.0275	1.1667	2.2700	1.3100
S.e	1.0430	8.6313	4.1665	3.4540	2.7344	1.2025	1.0409	.0071	.4335	0.0000	[illegible]

(Dose unit=MG ,Time unit=HR ,Concentration unit=NG/ML)

(C)

(5 NOV 1984 17h54) Problem : SL800750/CHLORPROMAZ Page 1

Subjects	.500	1.000	2.000	3.000	4.000	6.000	8.000	10.000	24.000	27.000	32.000
1-1.C											
2-2.C											
3-3.C											
4-4.C											
5-5.C											
6-6.C											
Mean	1.1175	3.3000	5.3550	6.7050	4.1347	3.3367	2.3033	2.0720	2.0125	1.1567	.6400
S.e	.2901	1.3704	1.7475	1.4240	.9430	.7391	.7547	.6411	.8415	.2335	[illegible]

(Dose unit=MG ,Time unit=HR ,Concentration unit=NG/ML)

TABLE 49

Table 5 Zolpidem. Individual pharmacokinetic parameters obtained after a single oral administration of 20 mg zolpidem:

A = alone.

C = combined with 50 mg chlorpromazine.

Subjects	Cmax (ng.ml^{-1})		tmax (h)		t1/2 (h)		AUC$_{0-\infty}$ (ng.ml^{-1}.h)	
	A	C	A	C	A	C	A	C
JAM								
HAN								
MAS								
GLN								
COU								
JAC								
Mean	323.5	285.8	0.75	1.3	1.70	2.05	912	967
SEM	60.0	76.9	0.10	0.40	0.29	0.34	169	229

IBE.2

045--0172

TABLE 43

IMIPRAMINE

Table 1 : Individual plasma concentrations of SL 80.0750 after administration of a 20 mg oral dose as a capsule.

Without imipramine

[24 MAY 1984 17h12] Analyse : SL80 0750 IMIPRAMINE Page 1

Subjects	Times .500	1.000	2.000	4.000	6.000	8.000	10.000
1							
2							
3							
4							
5							
6							
Mean	169.3333	178.8000	213.8000	145.8000	53.6167	44.7268	24.8000
S.d	37.8644	35.1131	66.2449	34.5821	19.9787	15.7428	10.8668

(Dose units=MG ,Time units=H ,Concentration units=NG/ML)

With a 75 mg oral dose of imipramine

[23 MAY 1984 17h12] Analyse : SL80 0750 IMIPRAMINE Page 1

Subjects	Times .500	1.000	2.000	4.000	6.000	8.000	10.000
1							
2							
3							
4							
5							
6							
Mean	238.8000	206.3333	198.8000	166.3333	64.6667	32.1833	21.8400
S.d	89.3141	67.9405	33.4287	38.5741	19.3663	8.6229	9.4074

(Dose units=MG ,Time units=H ,Concentration units=NG/ML)

COUPEZ/
IBE04

TABLE 44

Table 2 - Individual pharmacokinetic parameters of SL 80.0750 obtained after administration of a single 20 mg oral dose of SL 80.0750-23N as a capsule without imipramine (A), and with administration of a 75 mg oral dose of imipramine as tablets (C)

Subject		t_{max} (h)	C_{max} (ng/ml)	$t_{1/2}$ (h)	AUC_{∞} (ng/ml.h)
1 VEL.E.	A				
	C				
2 VIT.D.	A				
	C				
3 FRA.R.	A				
	C				
4 CAP.M.	A				
	C				
5 SEL.P.	A				
	C				
6 DAE.G.	A				
	C				
Mean ± SEM	A	1.0 ± 0.2	257 ± 54	2.0 ± 0.3	1103 ± 340
	C	2.0 ± 0.7	296 ± 67	1.8 ± 0.2	1159 ± 206