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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-908

DEC 16

Lorex Pharmaceuticals
Attention: Keith Rotenberg, Ph.D.
P.O. Box 163
4930 Oakton Street
Skokie, Illinois 60077

Dear Dr. Rotenberg:

Reference is made to your new drug application dated January 26, 1989, submitted pursuant to section 505(b) of the Federal Food, Drug and Cosmetic Act for AMBIEN (zolpidem tartrate) tablets, NDA 19-908.

We also acknowledge receipt of and/or refer to your additional communications dated:

September 17, 1992	November 16, 1992 (2 submissions)
October 19, 1992	November 17, 1992
October 21, 1992	November 19, 1992
October 27, 1992	November 23, 1992
November 4, 1992	December 4, 1992 (2 submissions)
November 6, 1992	

We have completed our review of this application, as amended, including the submitted draft labeling and patient package insert (PPI), and we have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the final draft of labeling that accompanies this letter (as Attachment 1). Accordingly, the application, with the enclosed draft labeling, is approved, effective as of the date of this letter.

Labeling/PPI

Regarding labeling and the PPI, we refer to our meeting with you on 11-9-92 to discuss labeling and a PPI for Ambien. At this meeting, we focused on FDA's 11-4-92 drafts (faxed to you in preparation for this meeting) of these documents. We reached substantial but not complete agreement at this meeting. On 11-30-92, Dr. Laughren faxed you another version of these documents that incorporated all of the agreed upon changes and also contained proposals for those few remaining sections upon which we had not yet reached agreement. You responded with a 12-4-92 fax containing your counter-proposals for these documents. We found many of the additional revisions to be minor and acceptable, and we have incorporated these changes into the final drafts of these documents that accompany this letter. However, there remain 2 primary areas of disagreement: Indications and Usage, and Contraindications. You prefer an Indications and Usage section that does not include a

recommendation to re-evaluate patients needing therapy beyond 2-3 weeks and does not limit prescriptions to 1 month. Since we are in the process of trying to implement such changes for all hypnotics, we feel it is both fair and essential to obtain this language for Ambien at this stage. You also want to contraindicate Ambien during pregnancy, primarily for liability reasons. However, we do not believe there is a sufficient basis for such a contraindication. Consequently, the drafts of labeling and PPI that accompany this letter contain language in these sections not previously agreed to by you. In addition, there were some minor modifications proposed in your 12-4-92 draft that we did not consider acceptable and these have not been incorporated. We have also made some minor modifications not previously agreed to, none of which we expect to be controversial. The drafts of labeling and PPI contain bracketed comments that refer to which proposed modifications (12-4-92) were accepted, and which were not, and also refer to any additional minor modifications.

Several other labeling/PPI issues need comment:

-In a cover letter for the 12-4-92 fax, you asked that FDA reconsider a much shorter form of the PPI, despite the fact that we had reached agreement with you on 11-9-92 about a longer form. Given that we are attempting to implement a longer form for all hypnotics, we feel that it is both fair and essential that we persist in our requirement for the longer form of the PPI for Ambien.

-In our 11-9-92 meeting with you, we had asked you to prepare a 'Geriatric Use' subsection under Precautions, addressing the size of the elderly population studied in your development program and brief comments on what was found regarding safety. In the 12-4-92 fax, you indicated that you do not plan to add such a subsection. We continue to feel that such a subsection would be useful, and we ask that you prepare such a statement for inclusion in labeling after approval.

The final printed labeling (FPL) must be identical to the draft labeling/PPI under Attachment 1. Marketing the product with FPL that is not identical to the draft labeling under Attachment 1 may render the product misbranded and an unapproved new drug.

Please submit twelve copies of the FPL to FDA as soon as available. Seven of the copies should be individually mounted on heavy-weight paper or similar material. The submission should be designated for administrative purposes as "FPL for approved NDA 19-908." Approval of this supplement by FDA is not required before the labeling may be used. Should additional information relating to the safety and effectiveness of this drug product become available, further revision of the labeling may be required.

Unit-of-use Packaging

While we acknowledge your arguments against the implementation of unit-of-use packaging for Ambien, we still intend to pursue such packaging since we consider it to be in the public interest. Nevertheless, we do not feel that the approval of this NDA should be held up on this basis. Consequently, we do not object to your plans for alternative packaging for Ambien at the present time.

Please submit one market package of the drug product when it is available.

Expiration Dating

On March 13, 1992, you were informed by Dr. Stanley Blum of this Division that your stability data supported a two (2) year expiration date for the 5 and 10 mg tablets. However, in a November 6, 1992 submission, you requested an extension of the expiration date from two (2) years to three (3) years. We have concluded that the available data do not support an extension of the expiration date to three (3) years.

The expiration date may be extended pursuant to 21 CFR 314.70(d)(5). The full shelf-life data (e.g., 3 years) obtained according to the stability protocol approved as part of the application must be submitted, and the expiration date change described, in an annual report.

Methods Validation

The validation of the analytical methods has not been completed for this application. We will expect your full cooperation in resolving any problems that may arise.

Advertising Copy

Please submit, in duplicate, the advertising copy which you intend to use in your proposed introductory promotional and/or advertising campaign. Please submit one copy to the Division of Neuropharmacological Drug Products, and the second copy to the Division of Drug Marketing, Advertising and Communications, HFD-240, Room 11B-06, 5600 Fishers Lane, Rockville, Maryland 20857. Please submit all proposed materials in draft or mock-up form, not final print. Also, please do not use form FD-2253 for this submission; this form is for routine use, not proposed materials.

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

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

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-908

APR 21 1992

Lorex Pharmaceuticals
Attention: Keith Rotenberg, Ph.D.
P.O. Box 16[illegible]
4930 Oakton Street
Skokie, Illinois 60077

Dear Dr. Rotenberg:

Reference is made to your new drug application dated January 26, 1989 submitted pursuant to section 505(b) of the Federal Food, Drug and Cosmetic Act for Ambien (zolpidem tartrate) tablets, NDA 19-908.

We also acknowledge receipt of your additional communications dated:

March 13, 1989	April 20, 1989	September 13, 1989
October 19, 1989	November 8, 1989	February 12, 1990
February 19, 1990	March 22, 1990	April 25, 1991
March 6, 1991	February 18, 1991	February 26, 1991
March 6, 1991	March 7, 1991	March 8, 1991
March 15, 1991	May 17, 1991	May 23, 1991
June 20, 1991	June 26, 1991	July 16, 1991
July 24, 1991	August 2, 1991	August 7, 1991
August 14, 1991	August 26, 1991	September 6, 1991
October 15, 1991		

We have completed our review of this application and it is approvable. Before the application may be approved, however, we ask that you respond to the following requests:

1. Re-Analysis of Efficacy Data for LSH

In our review of study LSH we noted that the outcome is quite different depending on whether the between group analyses for the PSG variables 'sleep latency' and 'sleep efficiency' focus on the unadjusted scores or on each variable expressed as change from baseline. While the analyses of unadjusted scores produce a result suggesting approximately equal efficacy for the 10 and 15 mg doses, the analyses of change from baseline on these variables suggest a clear superiority for the 15 mg dose and raise a question about the efficacy of the 10 mg dose. Since studies LSH and LSH still provide support for the 10 mg dose, we are not opposed to recommending this as the initial dose for Ambien. However, given the questions raised by the conflicting results for LSH we recommend that labeling suggest 15 mg as a back-up dose for patients not responding adequately to 10 mg. We have modified the proposed labeling for Ambien accordingly.

Even though we believe this is a reasonable compromise, given the data available, we think it would be appropriate to more fully analyze LSH with regard to this question. In your analysis of LSH the comparison of groups on the basis of change from baseline was not done for the PSG variable 'number of awakenings' or for subjective variables 'sleep latency' and 'number of awakenings.' We ask that you provide such analyses. In addition, it may be useful to attempt other approaches to adjusting for the baseline differences, e.g., analysis of covariance, and we ask that you provide such analyses. Once you have more fully analyzed the data for LSH it will be necessary to modify the summary of this study in the Clinical Pharmacology section of labeling (see proposed labeling).

2. Labeling

Accompanying this letter (ATTACHMENT 1) is the Agency's proposal for the labeling of Ambien. We believe it presents a fair summary of the information available on the benefits and risks of Ambien.

We have proposed a number of changes to the draft labeling submitted in your May 17, 1991 amendment, and explanations for these changes are provided in the bracketed comments embedded within the proposed text. Division staff would be happy to discuss these proposed changes in detail, and we would be happy to meet with you to discuss any disagreements you might have with any part of the proposed labeling format or content.

3. Patient Package Insert (PPI)

There has been much concern recently about the misuse of hypnotics, particularly the use of these drugs for longer durations than is appropriate and their use in patients not adequately evaluated for the presence of underlying psychiatric or physical disorders that are manifested by insomnia. One remedy to this problem is to strengthen physician labeling for these products, which we are in the process of doing, and another is to fully inform patients about the safe use of these products. Consequently, we have also asked the manufacturers of all benzodiazepine hypnotics to add a patient package insert (PPI), and we are asking you to adopt the PPI that we have attached to the draft labeling for Ambien. This PPI should be prepared both in free standing form for distribution to patients and as a continuation of the physician package insert. We will also be asking you to prepare unit-of-use packaging for Ambien (see 8, Manufacturing and Controls), and when ready, we will want the PPI attached to this packaging to ensure patient distribution.

4. Safety Update

Our review of the safety of Ambien was based on data accumulated through June, 1988 and provided in your original submission, as well as postmarketing data provided in your June 28, 1991 amendment. You will need to submit a safety update including safety data accumulated since June, 1988. This safety update should include a line listing of deaths and adverse dropouts associated with the use of Ambien, along with case report forms for all such patients. It should also identify any previously unrecognized adverse events that appear to be causally related to the use of Ambien, and it should compare rates for important adverse events in the new database with the original database. This safety update should also include whatever additional postmarketing information is available to you regarding the safety experience with Ambien use in any countries where it is marketed.

5. World Literature Update

Prior to the approval of Ambien we require an updated report on the world's archival literature pertaining to the safety of Ambien. This report should include only literature not covered in your previous submissions. We need your warrant that you have reviewed this literature systematically, and in detail, and that you have discovered no finding that would adversely affect conclusions about the safety of Ambien. The report should also detail how the literature search was conducted, by whom (their credentials) and whether it relied on abstracts or full texts (including translations) of articles. The report should emphasize clinical data, but new findings in preclinical reports of potential significance should also be described. Should any report or finding be judged important, a copy (translated as required) should be submitted for our review.

In this regard, we note that we have recently become aware of a reference book [Sauvanet JP, Langer SZ, Morselli PL, eds. Imidazopyridines in Sleep Disorders. New York: Raven Press, 1988.] that reviewed a number of published studies involving zolpidem for which copies of the published papers appear not to have been included in the original NDA submission. Although we have not yet been able to obtain copies of the references in question, it would appear that these references may suggest a less favorable comparison of zolpidem with other agents, albeit at a higher dose than is currently being recommended, than was suggested by data submitted in the NDA. You were obligated to provide us with all published data for zolpidem that were available at the time of the original

submission; if we are in error on this matter, please direct us to where these references are included in the original application. If they were, in fact, not included, we would like to be reassured that they, as well as any other pertinent references, will be included in your literature update.

6. Foreign Regulatory Update/Labeling

We require a review of the status of all Ambien actions taken or pending before foreign regulatory authorities. Approval actions can be noted, but we ask that you describe in detail any and all actions taken that have been negative, supplying a full explanation of the views of all parties and the resolution of the matter. In addition, we ask that you provide us current foreign labeling for Ambien, along with English translations when needed. If Ambien labeling is uniform worldwide, it would, of course, be sufficient to provide only the English translation of that standard labeling.

7. Biopharmaceutics

Since your study of Ambien in patients with renal disease (IFR12) involved intravenous administration of zolpidem rather than a tablet, a definitive conclusion regarding the lack of effect of renal disease on the pharmacokinetics of zolpidem following an oral dose cannot be made. We recommend that you conduct a Phase 4 study in renal disease patients in which Ambien is administered orally.

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] in 15 minutes

8. Manufacturing and Controls

We cannot approve this application until satisfactory establishment inspection reports have been received for all facilities involved in the manufacture and packaging of the bulk drug and the drug product.

Also, as noted above and as communicated to Dr. Engel by Dr. Laughren of FDA on December 12, 1991, we ask that you plan to manufacture unit-of-use packaging that will provide for no more than a 10-day supply and that will include the PPI as part of the packaging. When this packaging is ready for distribution, it is our intention that this will become the

only form in which Ambien can be distributed on an outpatient basis. It is important for you to understand that this requirement must be fulfilled prior to the final approval of this application.

Since you were not planning on recommending any doses above 10 mg, you had no reason to develop a 15 mg tablet. Given that we are now proposing a maximum dose of 15 mg, we ask that you consider developing a 15 mg tablet. While dosing at 15 mg would obviously be possible by combining 5 and 10 mg tablets, this would not be particularly convenient and may be confusing for some patients.

9. Pharmacology

We have some concern about the finding of liposarcomas in the rat carcinogenicity study. While we have limited our response to describing the findings in labeling, you should be aware that this concern has not yet been completely resolved at the present time.

10. Final Printed Labeling

Please submit 12 copies of the final printed labeling that are identical to the draft copy. Should additional information relating to the safety and effectiveness of these drug products become available prior to our receipt of the final printed labeling, revision of that labeling may be required.

11. Advertising Copy and Final Printed Labeling

Please submit, in duplicate, the advertising copy which you intend to use in your proposed introductory promotional and/or advertising campaign. Please submit one copy to the Division of Neuropharmacological Drug Products (HFD-120), and the second copy to the Division of Drug Advertising and Labeling, HFD-240, 11B-06, 5600 Fishers Lane, Rockville, Maryland 20857. Please submit all proposed materials in draft or mock-up form, not final print. Also, please do not use form FD-2253 for this submission; this form is for routine use, not proposed materials.

In accordance with the policy described in Section 314.102(d) of the new drug regulations and in the Center for Drugs and Biologics Staff Manual Guide CDB 4820.6, you may request an informal conference with the division to discuss what further steps you need to secure approval. The meeting is to be requested at least 15 days in advance. Alternatively, you may choose to receive such a report via a telephone call. Should you wish this conference or a telephone report, please call Mr. Merril Mille, Regulatory Management Officer, at (301) 443-3830.

Within 10 days after the date of this letter, you are required to amend the application, or notify us of your intent to file an amendment, or follow one of the other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ATTACHMENTS

CC: ORIG NDA
HFD-120
HFD-80
HFD-100/RTemple
HFD-120/PLeber
HFD-120/DCollins/TLaughren:
HFD-120/AWilk/GFitzgerald:
HFD-120/PMaturu/SElum:
HFD-120/MMille:8/5/91,11/21/91;12/3/91;4/9/92 mjm
HFD-420/DGordin/JHunt:11/27/91
HFD-632
HFD-730
HFD-713/RSrinivasan/ENevius:
HFC-130/JAllen
SPELLCHECK:11/21/91
DT:8/5/91/mjm
REVISED:Laughren/11-19-91;12/16/91 TL;4/3/92 TL
FT:12/3/91/mjm

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NDA APPROVABLE

ATTACHMENT 1

FINAL LABELING PROPOSAL

Ambien
(Zolpidem Tartrate Tablets)

[When the scheduling of Ambien is finalized, please insert classification symbol in the top right hand corner of the labeling.]

DESCRIPTION

Ambien (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:

[Insert structure here.]

Zolpidem tartrate is a white to off-white crystalline powder that is sparingly soluble in water, alcohol, and propylene glycol. It has a molecular weight of 764.88.

Each Ambien tablet includes the following inactive ingredients: hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate, titanium dioxide, FD&C Red No. 40 (5 mg strength only).

CLINICAL PHARMACOLOGY

Pharmacodynamics

Subunit modulation of the $GABA_a$ receptor chloride channel macromolecular complex is hypothesized to be responsible for sedative, anticonvulsant, anxiolytic and myorelaxant drug properties. The major modulatory site of the $GABA_a$ receptor complex is located on its α (alpha) subunit and is referred to as the benzodiazepine (BZ) or omega (ω) receptor. At least three subtypes of the (ω) receptor have been identified.

While zolpidem is an hypnotic agent with a chemical structure unrelated to benzodiazepines, barbiturates or other drugs with known hypnotic properties, it interacts with a GABA-BZ receptor complex and shares some of the pharmacological properties of the benzodiazepines. In contrast to the benzodiazepines, which non-

selectively bind to and activate all three omega receptor subtypes, zolpidem in vitro binds the (ω_1) receptor preferentially. The (ω_1) receptor is found primarily on the Lamina IV of the sensorimotor cortical regions, substantia nigra (pars reticulata), cerebellum molecular layer, olfactory bulb, ventral thalamic complex, pons, inferior colliculus and globus pallidus. This selective binding of zolpidem on the (ω_1) receptor is not absolute, but it may explain the relative absence of myorelaxant and anticonvulsant effects in animal studies as well as the preservation of deep sleep (stage 3-4) in human studies of zolpidem at hypnotic doses.

Pharmacokinetics

The pharmacokinetic profile of AMBIEN is characterized by rapid absorption from the GI tract and a short elimination half-life ($T_{\frac{1}{2}}$) in healthy subjects. In a single dose crossover study in 45 healthy subjects administered 5 and 10 mg zolpidem tartrate tablets, the mean peak concentrations (C_{max}) were 59 (range 29-113) and 121 (range 58-272) ng/ml, respectively, occurring at a mean time (t_{max}) of 1.6 hours for both. The mean AMBIEN elimination half-life was 2.6 (range: 1.4-4.5) and 2.5 (1.4-3.8) hours, for the 5 and 10 mg tablets, respectively. AMBIEN is converted to inactive metabolites that are eliminated primarily by renal excretion. AMBIEN demonstrated linear kinetics in the dose range of 5 to 20 mg. Total protein binding was found to be 92.5 ± 0.1% and remained constant, independent of concentration between 40 and 790 ng/ml. Zolpidem did not accumulate in young adults following nightly dosing with 20 mg zolpidem tartrate tablets for 2 weeks.

A food effect study in 30 healthy male volunteers compared the pharmacokinetics of AMBIEN 10 mg when administered while fasting or 20 minutes after a meal. Results demonstrated that with food mean AUC and C_{max} were decreased by 15% and 25%, respectively, while mean T_{max} was prolonged by 60% (from 1.4 to 2.2 hours). The half-life remained unchanged. These results suggest that, for faster sleep onset, AMBIEN should not be administered with or immediately after a meal.

In the elderly, the dose for AMBIEN should be 5 mg (see PRECAUTIONS and DOSAGE AND ADMINISTRATION). This recommendation is based on several studies in which the mean C_{max}, $T_{\frac{1}{2}}$ and AUC were significantly increased when compared to results in young adults. In one study of 8 elderly subjects (>70 years), the means for C_{max}, $T_{\frac{1}{2}}$ and AUC significantly increased by 50% (255 vs 384 ng/ml), 32% (2.2 vs 2.9 hr) and 64% (955 vs 1,562 ng·hr/ml), respectively, as compared to younger adults (20-40 yrs) following a single 20 mg oral zolpidem dose. AMBIEN did not accumulate in elderly subjects following nightly oral dosing of 10 mg for one week.

The pharmacokinetics of AMBIEN in eight patients with chronic hepatic insufficiency were compared to results in healthy subjects.

Following a single 20 mg oral zolpidem dose, mean C_{max} and AUC were found to be 2 times (250 vs 499 ng/ml) and 5 times (788 vs 4,203 ng·hr/ml) higher, respectively, in the hepatically compromised patients. T_{max} did not change. The mean half-life in cirrhotic patients of 9.9 hrs (range: 4.1-25.8 hrs) was greater than that observed in normals of 2.2 hrs (range: 1.6-2.4 hrs). Dosing should be modified accordingly in patients with hepatic insufficiency. (see PRECAUTIONS and DOSAGE and ADMINISTRATION).

[Please note that the AUC units are expressed incorrectly in the following paragraph of your 12-4-92 draft.]

The pharmacokinetics of AMBIEN were studied in 11 patients with end stage renal failure (mean CrCl = 6.5 ± 1.5 ml/min) undergoing hemodialysis three times a week, who were dosed with zolpidem 10 mg orally each day for 14 or 21 days. No statistically significant differences were observed for C_{max}, T_{max}, half-life and AUC between the first and last day of drug administration when baseline concentrations adjustments were made. On day 1, C_{max} was 172 ± 29 ng/ml (range: 46-344 ng/ml). After repeated dosing for 14 or 21 days, C_{max} was 203 ± 32 ng/ml (range: 28-316 ng/ml). On day 1, T_{max} was 1.7 ± 0.3 hr (range: 0.5-3.0 hr); after repeated dosing T_{max} was 0.8 ± 0.2 hr (range: 0.5-2.0 hr). This variation is accounted for by noting that last day serum sampling began 10 hours after the previous dose, rather than after 24 hours. This resulted in residual drug concentration and a shorter period to reach maximal serum concentration. On day 1, $T_{\frac{1}{2}}$ was 2.4 ± 0.4 hrs (range: 0.4-5.1 hrs). After repeated dosing, $T_{\frac{1}{2}}$ was 2.5 ± 0.4 hrs (range: 0.7 - 4.2 hrs). AUC was 796 ± 159 ng·hr/ml after the first dose and 818 ± 170 ng·hr/ml after repeated dosing. Zolpidem was not hemodializable. No accumulation of unchanged drug appeared after 14 or 21 days. AMBIEN pharmacokinetics were not significantly different in renally impaired patients. No dosage adjustment is necessary in patients with compromised renal function. As a general precaution, these patients should be closely monitored.

Postulated Relationship Between Elimination Rate of Hypnotics and their Profile of Common Untoward Effects

[Please note that we have adopted the changes in the next to last sentence of the following paragraph, as suggested in your 12-4-92 draft. However, we have not added your final sentence on daytime anxiety; as discussed at our 11-9-92 meeting, we feel that the trials from which the referenced data were obtained lacked sensitivity, and thus, it would not be informative to report these negative findings.]

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. Ambien has a short half-life and no active metabolites. 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 other rapidly eliminated hypnotics, namely, increased wakefulness during the last third of the night, and the appearance of increased signs of daytime anxiety. Increased wakefulness during the last third of the night as measured by polysomnography has not been observed in clinical trials with Ambien.

Controlled Trials Supporting Efficacy and Safety

Transient Insomnia

Normal adults experiencing transient insomnia (n=462) 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 objective (polysomnographic) measures of sleep latency, sleep duration, and number of awakenings

Chronic Insomnia

> [We have made several of the changes in this paragraph suggested in your 12-4-92 draft, however, we have not deleted information regarding the 15 mg dose. The experiment included a 15 mg group, and although 15 mg is not a recommended dose, the prescriber is entitled to know the full results of this study.]

Adult outpatients with chronic insomnia (n=75) were evaluated in a double-blind, parallel group, 5-week trial comparing 2 doses of zolpidem tartrate (10 and 15 mg) and placebo. On objective (polysomnographic) measures of sleep latency and sleep efficiency, zolpidem 15 mg was superior to placebo for all 5 weeks; zolpidem 10 mg was superior to placebo on sleep latency for the first 4 weeks and on sleep efficiency for weeks 2 and 4. Zolpidem was comparable to placebo on number of awakenings at both doses studied.

> [We have made several of the changes in this paragraph suggested in your 12-4-92 draft, however , we have not deleted

information regarding the 15 mg dose, for the same reason noted above.]

Adult outpatients (n=141) 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 mg was superior to placebo on a subjective measure of sleep latency for all 4 weeks, and on subjective measures of total sleep time, number of awakenings, and sleep quality for the first 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 the first week, and on number of awakenings and sleep quality for the first 2 weeks.

Next Day Residual Effects

[We have accepted some, but not all, of your 12-4-92 proposed modifications for this paragraph.]

There was no evidence of residual next-day effects seen with Ambien in several studies utilizing the Multiple Sleep Latency Test (MSLT), the Digit Symbol Substitution Test (DSST), and patient ratings of alertness. In one study involving elderly patients, there was a small but statistically significant decrease in one measure of performance, the DSST, but no impairment was seen in the MSLT in this study.

Rebound Effects

[We have largely accepted your 12-4-92 proposed modification of this paragraph, however, we have also made a minor modification of our own.]

There was no objective (polysomnographic) evidence of rebound insomnia at recommended doses seen in studies evaluating sleep on the nights following discontinuation of AMBIEN. There was subjective evidence of impaired sleep in the elderly on the first post-treatment night at doses above the recommended elderly dose of 5 mg.

Memory Impairment

[We have largely accepted your 12-4-92 proposed modification of this paragraph, however, we have also made minor modifications of our own.]

Two small studies (n=6 and n=9) utilizing objective measures of memory yielded little evidence for memory impairment following the administration of Ambien. There was subjective evidence from adverse event data for anterograde amnesia occurring in association with the administration of Ambien predominantly at doses above 10 mg.

Effects on Sleep Stages

In studies that measured the percentage of sleep time spent in each sleep stage, AMBIEN has generally been shown to preserve sleep stages. Sleep time spent in stage 3-4 (deep sleep) was found comparable to placebo with only inconsistent, minor changes in REM (paradoxical) sleep at the recommended dose.

INDICATIONS AND USAGE

[We do not agree with the modifications proposed in your 12-4-92 draft, and we have left this section as written in our 11-30-92 draft.]

AMBIEN (zolpidem tartrate) is indicated for the short-term treatment of insomnia. Hypnotics should generally be limited to 7-10 days of use, and re-evaluation of the patient is recommended if they are to be taken for more than 2-3 weeks.

AMBIEN should not be prescribed in quantities exceeding a 1-month supply (see WARNINGS).

AMBIEN has been shown to decrease sleep latency and increase the duration of sleep for up to 5 weeks in controlled clinical studies (see CLINICAL PHARMACOLOGY).

CONTRAINDICATIONS

[We do not agree with the modifications proposed in your 12-4-92 draft. We continue to believe that there is not a sufficient basis to contraindicate Ambien in pregnancy. Consequently, we have left this section as written in our 11-30-92 draft.]

None known.

WARNINGS

[We have added the slight modification to the first paragraph of this section proposed in your 12-4-92 draft.]

Since sleep disturbances may be the presenting manifestation of a physical and/or psychiatric disorder, symptomatic treatment of insomnia should be initiated only after a careful evaluation of the patient. 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 which should be evaluated. Worsening of insomnia or the emergence of new thinking or behavior abnormalities may be

the consequence of an unrecognized psychiatric or physical disorder. Such findings have emerged during the course of treatment with sedative/hypnotic drugs, including 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, especially in the elderly.

A variety of abnormal thinking and behavior changes have been reported to occur in association with the use of sedative/hypnotics. Some of these changes may be characterized by decreased inhibition (e.g., aggressiveness and extroversion that seemed out of character), similar to effects produced by alcohol and other CNS depressants. Other reported behavioral changes have included bizarre behavior, agitation, hallucinations, and depersonalization. Amnesia and other neuropsychiatric symptoms may occur unpredictably. In primarily depressed patients, worsening of depression, including suicidal thinking, has been reported in association with the use of sedative/hypnotics.

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.

Following the rapid dose decrease or abrupt discontinuation of sedative/hypnotics, there have been reports of signs and symptoms similar to those associated with withdrawal from other CNS-depressant drugs (see DRUG ABUSE AND DEPENDENCE).

AMBIEN, like other sedative/hypnotic drugs, has CNS-depressant effects. Due to the rapid onset of action, AMBIEN should only be ingested immediately prior to going to bed. 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. AMBIEN showed additive effects when combined with alcohol and should not be taken with alcohol. Patients should also be cautioned about possible combined effects with other CNS-depressant drugs. Dosage adjustments may be necessary when AMBIEN is administered with such agents because of the potentially additive effects.

PRECAUTIONS

General

Use in the Elderly and/or Debilitated Patients - Impaired motor and/or cognitive performance after repeated exposure or unusual sensitivity to sedative/hypnotic drugs is a concern in the treatment of elderly and/or debilitated patients. Therefore, the recommended AMBIEN dosage is 5 mg in such patients (see DOSAGE AND ADMINISTRATION) to decrease the possibility of side effects. These patients 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 sedative/hypnotics have the capacity to depress respiratory drive. Data in end stage renal failure patients repeatedly treated with AMBIEN did not demonstrate drug accumulation or alterations in pharmacokinetic parameters. No dosage adjustment in renally impaired patients is required, however, these patients should be closely monitored. (see PHARMACOKINETICS). A study in subjects with hepatic impairment did reveal prolonged elimination in this group, 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

> [We have made the modifications to this paragraph suggested in your 12-4-92 draft.]

Patient information is printed at the end of this insert. To assure safe and effective use of Ambien, this information and instructions provided in the patient information section should be discussed with patients.

Laboratory Tests

There are no specific laboratory tests recommended.

Drug Interactions

CNS Active Drugs - AMBIEN was evaluated in healthy volunteers in single dose interaction studies for several CNS 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. The lack of a drug interaction following single dose administration does not predict a lack following chronic administration.

An additive effect on psychomotor performance between alcohol and zolpidem was demonstrated.

Since the systematic evaluations of AMBIEN 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. Zolpidem had no effect on digoxin kinetics and did not affect prothrombin time when given with warfarin in normal subjects. Zolpidem's sedative/hypnotic effect was reversed by flumazenil, however, no significant alterations in zolpidem pharmacokinetics were found.

Drug/Laboratory Test Interactions

Zolpidem is not known to interfere with commonly employed clinical laboratory tests.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Zolpidem was administered to rats and mice for two years at dietary dosages of 4, 18, and 80 mg/kg/day. In mice, these doses are 26-520 times or 2-35 times the maximum 10 mg human dose on a mg/kg or mg/m^2 basis, respectively. In rats these doses are 43-876 times or 6-115 times the maximum 10 mg human dose on a mg/kg or mg/m^2 basis, respectively. No evidence of carcinogenic potential was observed in mice. Renal liposarcomas were seen in 4/100 rats (3 males, 1 female) receiving 80 mg/kg/day and a renal lipoma was observed in one male rat at the 18 mg/kg/day dose. Incidence rates of lipoma and liposarcoma for zolpidem were comparable to those seen in historical controls and the tumor findings are thought to be a spontaneous occurrence.

Mutagenesis: Zolpidem did not have mutagenic activity in several tests including the Ames test, genotoxicity in mouse lymphoma cells *in vitro*, chromosomal aberrations in cultured human lymphocytes, unscheduled DNA synthesis in rat hepatocytes *in vitro*, and the

micronucleus test in mice.

Impairment of Fertility: In a rat reproduction study, the high dose (100 mg base/kg) of zolpidem resulted in irregular estrus cycles and prolonged precoital intervals, but there was no effect on male or female fertility after daily oral doses of 4-100 mg base/mg or 5-130 times the recommended human doses in mg/m^2. No effects on any other fertilily parameters were noted.

Pregnancy:

[As discussed under Contraindications, we do not believe there is a sufficient basis to contraindicate Ambien in pregnancy. Consequently, we have not adopted your 12-4-92 proposed modifications for this section.]

Teratogenic effects: Pregnancy Category B.

Studies to assess the effects of zolpidem on human reproduction and development have not been conducted.

Teratology studies were conducted in rats and rabbits.

In rats, adverse maternal and fetal effects occurred at 20 and 100mg base/kg and included dose related maternal lethergy and ataxia and a dose related trend to incomplete ossification of fetal skull bones. Underossification of various fetal bones indicates a delay in maturation and is often seen in rats treated with sedative/hypnotic drugs. There were no teratogenic effects after zolpidem administration. The no effect dose for maternal or fetal toxicity was 4mg base/kg or 5 times the maximum human dose on a mg/m^2 basis.

In rabbits, dose related maternal sedation and decreased weight gain occurred at all doses tested. At the high dose, 16 mg base/kg, there was an increase in postimplantation fetal loss and underossification of sternebrae in viable fetuses. These fetal findings in rabbits are often secondary to reductions in maternal weight gain. There were no frank teratogenic effects. The no effect dose for fetal toxicity was 4mg base/kg or 7 times the maximum human dose on a mg/m^2 basis.

Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Non-teratogenic effects: Studies to assess the effects on children whose mothers took zolpidem during pregnancy have not been conducted. However, children born of mothers taking sedative/hypnotic drugs may be at some risk for withdrawal symptoms from the drug during the postnatal period. In addition, neonatal flaccidity has been reported in infants born of mothers who

received sedative/hypnotic drugs during pregnancy.

Labor and Delivery

AMBIEN has no established use in labor and delivery.

Nursing Mothers

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.

In addition, in a rat study, zolpidem inhibited the secretion of milk. The no effect dose was 4 mg base/kg or 6 times the recommended human dose in mg/m^2.

The use of AMBIEN in nursing mothers is not recommended.

Pediatric Use

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

ADVERSE REACTIONS

Associated with Discontinuation of Treatment

Approximately 4% of 1,701 patients who received zolpidem at all doses (1.25 to 90 mg) in U.S. premarketing clinical trials discontinued treatment because of an adverse clinical event. Events most commonly associated with discontinuation from US trials were daytime drowsiness (0.5%), dizziness (0.4%), headache (0.5%), nausea (0.6%) and vomiting (0.5%).

Approximately 6% of 1,320 patients who received zolpidem at all doses (5 to 50 mg) in similar foreign trials discontinued treatment because of an adverse event. Events most commonly associated with discontinuation from these trials were daytime drowsiness (1.6%), amnesia (0.6%), dizziness (0.6%), headache (0.6%), and nausea (0.6%).

Incidence in Controlled Clinical Trials

The tables below enumerate treatment emergent adverse event frequencies that were observed at an incidence equal to 1% or greater among patients with insomnia who received AMBIEN in U.S. placebo-controlled trials. Events reported by investigators were classified utilizing a modified World Health Organization (WHO) dictionary of preferred terms for the purpose of establishing event

frequencies. The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice, in which patients characteristics and other factors differ from those that prevailed in these clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigators involving related drug products and uses, since each group of drug trials is conducted under a different set of conditions. However, the cited figures provide the physician with a basis for estimating the relative contribution of drug and nondrug factors to the incidence of side effects in the population studied.

The following table was derived from a pool of 11 placebo controlled short term U.S. efficacy trials involving zolpidem in doses ranging from 1.25 to 20 mg. The table is limited to data from doses up to and including 10 mg, the highest dose recommended for use.

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

Body System Adverse Event+	Zolpidem (≤ 10 mg) (N=685)	Placebo (N=473)
Central and Peripheral Nervous System		
Headache	7	6
Drowsiness	2	-
Dizziness	1	-
Gastrointestinal System		
Nausea	2	3
Diarrhea	1	-
Musculoskeletal System		
Myalgia	1	2

+Events reported by at least 1% of AMBIEN patients are included.

The following table was derived from a pool of three placebo controlled long term efficacy trials involving AMBIEN. These trials involved patients with chronic insomnia who were treated for 28-35 nights with zolpidem at doses of 5, 10 or 15 mg. The table is limited to data from doses up to and including 10 mg, the highest dose recommended for use. The table includes only adverse events occurring at an incidence of at least 1% for zolpidem patients.

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

Body System/Placebo Adverse Event+	Zolpidem (≤ 10 mg) (N=152)	Placebo (N=161)
Autonomic Nervous System		
Dry Mouth	3	1
Body as a Whole		
Allergy	4	1
Back Pain	3	2
Influenza-like Symptoms	2	-
Chest Pain	1	-
Fatigue	1	2
Cardiovascular System		
Palpitation	2	-
Central and Peripheral Nervous System		
Headache	19	22
Drowsiness	8	5
Dizziness	5	1
Lethargy	3	1
Drugged Feeling	3	-
Light-Headed	2	1
Depression	2	1
Abnormal Dreams	1	-
Amnesia	1	-
Anxiety	1	1
Nervousness	1	3
Sleep Disorder	1	-
Gastrointestinal System		
Nausea	6	6
Dyspepsia	5	6
Diarrhea	3	2
Abdominal Pain	2	2
Constipation	2	1
Anorexia	1	1
Vomiting	1	1
Immunologic System		
Infection	1	1
Musculoskeletal System		
Myalgia	7	7
Arthralgia	4	4
Respiratory System		
Upper Respiratory Infection	5	6
Sinusitis	4	2
Pharyngitis	3	1
Rhinitis	1	3
Skin and Appendages		
Rash	2	1
Urogenital System		
Urinary Tract Infection	2	2

+Events reported by at least 1% of patients treated with AMBIEN.

Dose-Relationship for Adverse Events - There is evidence from dose comparison trials suggesting a dose-relationship for many of the adverse events associated with zolpidem use, particularly for certain CNS and gastrointestinal adverse events.

Most Commonly Observed Adverse Events in Controlled Trials - During short term treatment (up to 10 nights) with AMBIEN at doses up to 10 mg, the most commonly observed adverse events associated with the use of zolpidem and seen at statistically significant differences from placebo treated patients were: drowsiness (reported by 2% of zolpidem patients), dizziness (1%), and diarrhea (1%). During longer term treatment (28-35 nights) with zolpidem at doses up to 10 mg, the most commonly observed adverse events associated with the use of zolpidem and seen at statistically significant differences from placebo treated patients were: dizziness (5%), and drugged feelings (3%).

Adverse Event Incidence Across the Entire Pre-approval Database

AMBIEN was administered to 3,021 subjects in clinical trials throughout the U. S., Canada and Europe. Treatment emergent adverse events associated with clinical trial participation were recorded by clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals experiencing treatment emergent adverse events, similar types of untoward events were grouped into a smaller number of standardized event categories and classified utilizing a modified World Health Organization (WHO) dictionary of preferred terms. The frequencies presented, therefore, represent the proportions of the 3,021 individuals exposed to zolpidem who experienced an event of the type cited on at least one occasion while receiving zolpidem. All reported treatment-emergent adverse events are included, except those already listed in the table above of adverse events in long term placebo controlled studies, those coding terms that are so general as to be uninformative and those events where a drug cause was remote. It is important to emphasize that, although the events reported did occur during treatment with AMBIEN, they were not necessarily caused by it.

> [We have made the slight modification to this paragraph suggested in your 12-4-92 draft.]

Adverse events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring in greater than 1/100 subjects; infrequent adverse events are those occurring in 1/100 to 1/1,000 patients; rare events are those occurring in less than 1/1,000 patients.

Autonomic Nervous System: Infrequent: increased sweating, pallor, postural hypotension Rare: altered saliva, flushing, glaucoma,

hypotension, impotence, syncope, tenesmus

Body as a Whole: Infrequent: asthenia, edema, falling, fever, malaise, trauma Rare: allergic reaction, allergy aggravated, abdominal body sensation, anaphylactic shock, face edema, hot flashes, increased ESR, pain, restless legs, rigors, tolerance increased, weight decrease

Cardiovascular System: Infrequent: Cerebrovascular disorder, hypertension, tachycardia Rare: Arrhythmia, arteritis, circulatory failure, extrasystoles, hypertension aggravated, myocardial infarction, phlebitis, pulmonary embolism, pulmonary edema, varicose veins, ventricular tachycardia

Central and Peripheral Nervous System: Frequent: ataxia, confusion, euphoria, insomnia, vertigo Infrequent: agitation, decreased cognition, detached, difficulty concentrating, dysarthria, emotional lability, hallucination, hypoesthesia, migraine, paraesthesia, sleeping (after daytime dosing), stupor, tremor Rare: abnormal thinking, aggressive reaction, appetite increased, decreased libido, delusion, dementia, depersonalization, dysphasia, feeling strange, hypotonia, hysteria, illusion, intoxicated feeling, leg cramps, manic reaction, neuralgia, neuritis, neuropathy, neurosis, panic attacks, paresis, personality disorder, somnambulism, suicide attempts, tetany, yawning.

Gastro-Intestinal System: Infrequent: constipation, dysphagia, flatulence, gastroenteritis, hiccup, Rare: enteritis, eructation, esophagospasm, gastritis, hemorrhoids, intestinal obstruction, rectal hemorrhage, tooth caries

Hematologic and Lymphatic System: Rare: anemia, hyperhemoglobinemia, leukopenia, lymphadenopathy, macrocytic anemia, purpura

Immunologic System: Rare: abscess, herpes simplex, herpes zoster, otitis externa, otitis media

Liver and Biliary System: Infrequent: increased SGPT Rare: abnormal hepatic function, bilirubinemia, increased SGOT

Metabolic and Nutritional: Infrequent: hyperglycemia Rare: gout, hypercholesteremia, hyperlipidemia, increased BUN, periorbital edema, thirst, weight decrease

Musculoskeletal System: Infrequent: arthritis Rare: arthrosis, muscle weakness, sciatica, tendinitis

Reproductive System: Infrequent: menstrual disorder, vaginitis Rare: breast fibroadenosis, breast neoplasm, breast pain

Respiratory System: Infrequent: bronchitis, coughing, dyspnea Rare: bronchospasm, epistaxis, hypoxia, laryngitis, pneumonia

Skin and Appendages: Rare: acne, bullous eruption, dermatitis, furunculosis, injection site inflammation, photosensitivity reaction, urticaria

Special Senses: Frequent: diplopia, vision abnormal Infrequent: eye irritation, scleritis, taste perversion, tinnitus Rare: corneal ulceration, eye pain, lacrimation abnormal, photopsia

Urogenital System: Infrequent: cystitis, urinary incontinence Rare: acute renal failure, dysuria, micturition frequency, polyuria, pyelonephritis, renal pain, urinary retention

DRUG ABUSE AND DEPENDENCE

[We have made the slight modifications to this section suggested in your 12-4-92 draft, and added a slight modification of our own.]

Ambien tablets have not yet been scheduled.

Abuse and Dependence

Studies of abuse potential in former drug abusers found that the effects of single doses of zolpidem tartrate 40 mg were similar, but not identical, to diazepam 20 mg, while zolpidem tartrate 10 mg was difficult to distinguish from placebo.

Sedative/hypnotics have produced withdrawal signs and symptoms following abrupt discontinuation. These reported symptoms range from mild dysphoria and insomnia to a withdrawal syndrome that may include abdominal and muscle cramps, vomiting, sweating, tremors, and convulsions. The U.S. clinical trial experience from zolpidem does not reveal any clear evidence for a withdrawal syndrome. Nevertheless, the following adverse events included in DSM-III-R criteria for uncomplicated sedative/hypnotic withdrawal were reported during U.S. clinical trials following placebo substitution occurring within 48 hours following last zolpidem treatment: fatigue, nausea, flushing, lightheadedness, uncontrolled crying, emesis, stomach cramps, panic attack, nervousness, and abdominal discomfort. These reported adverse events occurred at an incidence of 1% or less. However, available data cannot provide a reliable estimate of the incidence, if any, of dependency, or the relationship of any dependency to dose and duration of treatment.

Because individuals with a history of addiction to, or abuse of, drugs or alcohol are at risk of habituation and dependence, they should be under careful surveillance when receiving zolpidem or any other hypnotic.

OVERDOSAGE

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 tartrate overdoses up to 400 mg (40 times the maximum recommended dose). Overdose cases involving multiple CNS depressant agents, including zolpidem, have resulted in more severe symptomatology, 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. Flumazenil may be useful. 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.

DOSAGE AND ADMINISTRATION

The dose of Ambien should be individualized.

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, 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.

HOW SUPPLIED

Ambien 5 mg tablets are capsule-shaped, pink, film-coated, identified with markings of "SN 5" on one side and "5401" on the other and supplied as:

NDC Number	Size
0025-5401-31	bottle of 100
0025-5401-51	bottle of 500
0025-5401-34	carton of 100 unit dose in blister paks

Ambien 10 mg tablets are capsule-shaped, white, film-coated, identified with markings of "SN 10" on one side and "5421" on the other and supplied as:

NDC Number	Size
0025-5421-31	bottle of 100
0025-5421-51	bottle of 500
0025-5421-34	carton of 100 unit dose in blister paks

Store below 86°F (30°C)

Caution: Federal law prohibits dispensing without prescription.

END OF LABELING

[We have modified the following paragraph as suggested in your 12-4-92 draft.]

The text of the patient information for Ambien is set forth below.

[In your 12-4-92 draft, you proposed a number of additional modifications to the PPI. Most of these modifications are acceptable, and we have incorporated them into this final draft of the PPI. However, 3 proposed changes were not acceptable. In particular, we have not added language recommending against use of Ambien during pregnancy, since as discussed earlier, we do not believe there is sufficient evidence for contraindicating such use. In addition, we have not added the sentence under 'Special Concerns' suggesting that none of these special problems are common for Ambien. There are insufficient data to support such a broad statement.]

INFORMATION FOR PATIENTS TAKING AMBIEN

Your doctor has prescribed AMBIEN to help you sleep. The following information is intended to guide you in the safe use of this medicine. It is not meant to take the place of your doctor's instructions. If you have any questions about AMBIEN tablets be sure to ask your doctor or pharmacist.

AMBIEN is used to treat different types of sleep problems, such as:

- trouble falling asleep
- waking up too early in the morning
- waking up often during the night

Some people may have more than one of these problems.

AMBIEN belongs to a group of medicines known as the "sedative/hypnotics," or simply, sleep medicines. There are many different sleep medicines available to help people sleep better. Sleep problems are usually temporary, requiring treatment for only a short time, usually 1 or 2 days up to 1 or 2 weeks. Some people have chronic sleep problems that may require more prolonged use of sleep medicine. However, you should not use these medicines for long periods without talking with your doctor about the risks and benefits of prolonged use.

SIDE EFFECTS

Most Common Side Effects

All medicines have side effects. Most common side effects of sleep medicines include:

- drowsiness
- dizziness
- lightheadedness
- difficulty with coordination

You may find that these medicines make you sleepy during the day. How drowsy you feel depends upon how your body reacts to the medicine, which sleep medicine you are taking, and how large a dose your doctor has prescribed. Day-time drowsiness is best avoided by taking the lowest dose possible that will still help you to sleep at night. Your doctor will work with you to find the dose of AMBIEN that is best for you.

To manage these side effects while you are taking this medicine:

- When you first start taking AMBIEN or any other sleep medicine until you know whether the medicine will still have some carryover effect in you the next day, use extreme care while doing anything that requires complete alertness, such as driving a car, operating machinery, or piloting an aircraft .

- NEVER drink alcohol while you are being treated with AMBIEN or any sleep medicine. Alcohol can increase the side effects of AMBIEN or any other sleep medicine.

- Do not take any other medicines without asking your doctor first. This includes medicines you can buy without a prescription. Some medicines can cause drowsiness and are best avoided while taking AMBIEN.

- Always take the exact dose of AMBIEN prescribed by your doctor. Never change your dose without talking to your doctor first.

SPECIAL CONCERNS

There are some special problems that may occur while taking sleep medicines.

Memory Problems

Sleep medicines may cause a special type of memory loss or "amnesia". When this occurs, a person may not remember what has happened for several hours after taking the medicine. This is usually not a problem since most people fall asleep after taking the medicine.

Memory loss can be a problem, however, when sleeping medicines are taken while traveling, such as during an airplane flight and the person wakes up before the effect of the medicine is gone. This has been called "traveler's amnesia".

Memory problems are not common while taking AMBIEN. In most instances, memory problems can be avoided if you take AMBIEN only

when you are able to get a full night's sleep (7 to 8 hours) before you need to be active again. Be sure to talk to your doctor if you think you are having memory problems.

Tolerance

When sleep medicines are used every night for more than a few weeks, they may lose their effectiveness to help you sleep. This is known as "tolerance". Sleep medicines should, in most cases, be used only for short periods of time, such as 1 or 2 days and generally no longer than 1 or 2 weeks. If your sleep problems continue, consult your doctor, who will determine whether other measures are needed to overcome your sleep problems.

Dependence

Sleep medicines can cause dependence, especially when these medicines are used regularly for longer than a few weeks or at high doses. Some people develop a need to continue taking their medicines. This is known as dependence or "addiction."

When people develop dependence, they may have difficulty stopping the sleep medicine. If the medicine is suddenly stopped, the body is not able to function normally and unpleasant symptoms (see "Withdrawal") may occur. They may find they have to keep taking the medicine either at the prescribed dose or at increasing doses just to avoid withdrawal symptoms.

All people taking sleep medicines have some risk of becoming dependent on the medicine. However, people who have been dependent on alcohol or other drugs in the past may have a higher chance of becoming addicted to sleep medicines. This possibility must be considered before using these medicines for more than a few weeks.

If you have been addicted to alcohol or drugs in the past, it is important to tell your doctor before starting AMBIEN or any sleep medicine.

Withdrawal

Withdrawal symptoms may occur when sleep medicines are stopped suddenly after being used da ly for a long time. In some cases, these symptoms can occur even if the medicine has been used for only a week or two.

In mild cases, withdrawal symptoms may include unpleasant feelings. In more severe cases, abdominal and muscle cramps, vomiting, sweating, shakiness, and rarely, seizures may occur. These more severe withdrawal symptoms are very uncommon.

Another problem that may occur when sleep medicines are stopped is known as "rebound insomnia". This means that a person may

have more trouble sleeping the first few nights after the medicine is stopped than before starting the medicine. If you should experience rebound insomnia, do not get discouraged. This problem usually goes away on its own after one or two nights.

If you have been taking AMBIEN or any other sleep medicine for more than 1 or 2 weeks, do not stop taking it on your own. Always follow your doctor's directions.

Changes in Behavior and Thinking

Some people using sleep medicines have experienced unusual changes in their thinking and/or behavior. These effects are not common. However, they have included:

- more outgoing or aggressive behavior than normal
- loss of personal identity
- confusion
- strange behavior
- agitation
- hallucinations
- worsening of depression
- suicidal thoughts

How often these effects occur depends on several factors, such as a person's general health, the use of other medicines, and which sleep medicine is being used. Clinical experience with AMBIEN suggests that it is uncommonly associated with these behavior changes.

It is also important to realize that it is rarely clear whether these behavior changes are caused by the medicine, an illness, or occur on their own. In fact, sleep problems that do not improve may be due to illnesses that were present before the medicine was used. If you or your family notice any changes in your behavior, or if you have any unusual or disturbing thoughts, call your doctor immediately.

Pregnancy

Sleep medicines may cause sedation of the unborn baby when used during the last weeks of pregnancy.

Be sure to tell your doctor if you are pregnant, if you are planning to become pregnant, or if you become pregnant while taking AMBIEN.

SAFE USE OF SLEEPING MEDICINES

To ensure the safe and effective use of AMBIEN or any other sleep medicine, you should observe the following cautions:

1. AMBIEN is a prescription medicine and should be used ONLY as directed by your doctor. Follow your doctor's instructions about how to take, when to take, and how long to take AMBIEN.

2. Never use AMBIEN or any other sleep medicine for longer than directed by your doctor.

3. If you notice any unusual or disturbing thoughts or behavior during treatment with AMBIEN or any other sleep medicine, contact your doctor.

4. Tell your doctor about any medicines you may be taking, including medicines you may buy without a prescription. You should also tell your doctor if you drink alcohol. DO NOT use alcohol while taking AMBIEN or any other sleep medicine.

5. Do not take AMBIEN or any other sleep medicine unless you are able to get a full night's sleep before you must be active again. For example, AMBIEN or any other sleep medicine should not be taken on an overnight airplane flight of less than 7 to 8 hours since "traveler's amnesia" may occur

6. Do not increase the prescribed dose of AMBIEN or any other sleep medicine unless instructed by your doctor.

7. When you first start taking AMBIEN or any other sleep medicine until you know whether the medicine will still have some carryover effect in you the next day, use extreme care while doing anything that requires complete alertness, such as driving a car, operating machinery, or piloting an aircraft .

8. Be aware that you may have more sleeping problems the first night or two after stopping AMBIEN or any other sleep medicine.

9. Be sure to tell your doctor if you are pregnant, if you are planning to become pregnant, or if you become pregnant while taking AMBIEN.

10. As with all prescription medicines, never share AMBIEN or any other sleep medicine with anyone else. Always store AMBIEN or any other sleep medicine in the original container out of reach of children.

11. AMBIEN works very quickly. You should only take AMBIEN right before you are going to bed and are ready to go to sleep.

Doc AMBENPPI.AP2