CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 76-062

***Name*:** Zolpidem Tartrate Tablets, 5 mg and 10 mg

***Sponsor*:** Par Pharmaceutical, Inc.

***Approval Date*:** April 23, 2007

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-062

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-062

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 76-062

Par Pharmaceutical, Inc.
Attention: Julie Szozda
Senior Associate, Regulatory Affairs
One Ram Ridge Road
Spring Valley, NY 10977

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated December 22, 2000, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Zolpidem Tartrate Tablets, 5 mg and 10 mg.

Reference is also made to the tentative approval letter issued by this office on April 26, 2002, and to your amendments dated March 17, August 16, August 28, September 13, and October 3, 2006; and April 18, 2007.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is approved, effective the date of this letter. The Division of Bioequivalence has determined your Zolpidem Tartrate Tablets, 5 mg and 10 mg, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug, Ambien® Tablets, 5 mg and 10 mg, respectively, of Sanofi Aventis US, LLC. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Division of Drug Marketing, Advertising, and Communications with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

{See appended electronic signature page}

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Robert L. West
4/23/2007 03:26:05 PM
for Gary Buehler

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-062

TENTATIVE APPROVAL LETTER

ANDA 76-062

APR 26 2002

Par Pharmaceutical, Inc.
Attention: Janis A. Picurro
One Ram Ridge Road
Spring Valley, NY 10977

Dear Madam:

This letter is a **correction** to our April 26, 2002 tentative approval letter. The November 11, 2001 amendment has been changed to November 30, 2001. In addition, the phrase "[the '938 patent]" has been added. This letter supercedes the April 26, 2002 letter.

This is in reference to your abbreviated new drug application dated December 22, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Zolpidem Tartrate Tablets, 5 mg and 10 mg.

Reference is also made to your amendments dated August 23, and November 30, 2001; and February 11, and March 11, 2002.

We have completed the review of this abbreviated application and have concluded that based upon the information you have presented to date, the drug is safe and effective for use as recommended in the submitted labeling. Therefore, the application is **tentatively approved.** This determination is based upon information available to the Agency at this time, (i.e., information in your application and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacture and testing of the drug product). The determination is subject to change on the basis of new information that may come to our attention.

The reference listed drug product (RLD) upon which you have based your application, Ambien Tablets of Lorex Pharmaceuticals, is currently subject to a period of patent protection which expires on October 21, 2006 (U.S. Patent No. 4,382,938 [the '938 patent]). Your application contains a Paragraph III Certification to the patent under Section 505(j)(2)

(A)(vii)(III) of the Act stating that you will not market this drug product prior to the expiration of the '938 patent. Therefore, final approval of your application may not be made effective pursuant to 21 U.S.C. 355(j)(5)(B)(ii) of the Act until the period has expired, i.e., currently October 21, 2006.

In order to reactivate this application prior to final approval, please submit a MINOR AMENDMENT - FINAL APPROVAL REQUESTED between 60 - 90 days prior to the date you believe your application will be eligible for final approval. This amendment should identify changes, if any, in the conditions under which the product was tentatively approved, and should include updated information such as labeling, chemistry, manufacturing, and controls data as appropriate. This amendment should be submitted even if none of these changes were made. This submission should be designated clearly in your cover letter as a MINOR AMENDMENT. In addition to this amendment, the Agency may request at any time prior to the final date of approval that you submit an additional amendment containing the information described above.

Failure to submit either or, if requested, both amendments may result in rescission of the tentative approval status of your application, or may result in a delay in the issuance of the final approval letter.

Any significant changes in the conditions outlined in this abbreviated application as well as changes in the status of the manufacturing and testing facilities' compliance with current good manufacturing practices (CGMPs) are subject to Agency review before final approval of the application will be made.

Please note that this drug product may not be marketed without final Agency approval under Section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under Section 501 of the Act and 21 U.S.C. 331(d). Also, until the Agency issues the final approval letter, this drug product will not be deemed approved for marketing under 21 U.S.C. 355 and will not be listed in the "Approved Drug Products with Therapeutic Equivalence Evaluations" list (the "Orange Book"), published by the Agency. Should you believe that there are grounds for issuing the final approval letter prior to October 21, 2006, you should amend your application accordingly.

Should you elect to make significant changes to the application, please categorize and submit your amendment according to office policy.

Please contact Sarah Ho, Pharm.D., Project Manager, at 301-827-5848, if you have questions concerning the status of the application or prior to submission of the amendments referenced above.

Sincerely yours,

Gary Buehler 4/26/02
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc: ANDA 76-062
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205

Endorsements:
HFD-629/G.Kang/
HFD-623/J.Fan/
HFD-617/S.Ho/ 4/30/02
HFD-613/L.Golson/
HFD-613/J.Grace/

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F/T by: SH 4/30/02

TENTATIVE APPROVAL - CORRECTION

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-062

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use zolpidem tartrate tablets safely and effectively. See full prescribing information for zolpidem tartrate tablets

Zolpidem tartrate tablets for oral administration
Initial US Approval: 1992

RECENT MAJOR CHANGES

Indications and Usage (1)	03/2007
Warnings and Precautions (5)	03/2007

INDICATIONS AND USAGE

Zolpidem tartrate tablets are indicated for the short-term treatment of insomnia characterized by difficulties with sleep initiation. Zolpidem tartrate tablets have been shown to decrease sleep latency for up to 35 days in controlled clinical studies. (1)

DOSAGE AND ADMINISTRATION

- Adult dose: 10 mg immediately before bedtime (2.1)
- Elderly/Debilitated patients/Hepatic Impairment: Initial dose of 5 mg (2.2)
- Downward dosage adjustment may be necessary when used with CNS depressants (2.3)
- Total daily dose should not exceed 10 mg (2.4)

DOSAGE FORMS AND STRENGTHS

5 mg and 10 mg tablets (3)

CONTRAINDICATIONS

Hypersensitivity to zolpidem tartrate or inactive ingredients (4.1)

WARNINGS AND PRECAUTIONS

- Reevaluate if insomnia persists after 7 to 10 days of use (5.1)
- Severe anaphylactic and anaphylactoid reactions have been reported (5.2)
- Abnormal thinking, behavior changes and complex behaviors such as sleep-driving have been reported (5.3)
- Pediatric patients with attention-deficit/hyperactivity disorder (ADHD): Hallucinations (7.4%) and other psychiatric and /or nervous system adverse events were observed frequently (5.6, 8.4)
- Depression: Worsening of depression or, suicidal thinking may occur. Prescribe the least amount feasible to avoid intentional overdose (5.3, 5.6)
- Withdrawal symptoms may occur with rapid dose reduction or discontinuation (5.4)
- CNS depressant effects, additive effects with CNS depressants (2.3, 5.5)
- Potential impairment of activities requiring complete mental alertness such as operating machinery or driving a motor vehicle, after ingesting the drug and the following day (5.5)
- Additive effects with alcohol; should not be taken with alcohol (5.5)
- Elderly/debilitated patients: Impaired motor, cognitive performance after repeated exposure, increased sensitivity (2.2, 5.6)
- Caution advised in patients with hepatic impairment, mild to moderate COPD, impaired drug metabolism or hemodynamic responses, mild to moderate sleep apnea (5.6)

ADVERSE REACTIONS

- Most commonly observed adverse events in studies with zolpidem (up to 10 mg) at statistically significant differences from placebo were:
  Short-term (<10 nights): Drowsiness, dizziness, and diarrhea
  Long-term (28 - 35 nights): Dizziness and drugged feelings (6.1)
- Dose relationship observed for adverse events especially CNS and GI events (6.1)
- Other adverse reactions, including serious adverse reactions, have been reported (6)

To report SUSPECTED ADVERSE REACTIONS, contact Par Pharmaceutical Companies, Inc. at 1-800-828-9393, or http://www.parpharm.com or FDA at 1-800-FDA-1088, or http://www.fda.gov

DRUG INTERACTIONS

- Imipramine: decreased alertness (7.1)
- Chlorpromazine: impaired alertness and psychomotor performance (7.1)
- Alcohol causes additive psychomotor impairment (7.1)
- Rifampin (CYP450) decreases exposure to, and effects of zolpidem (7.2)
- Sedative/hypnotic effect reversed by flumazenil (7.3, 10.2)

USE IN SPECIFIC POPULATIONS

- Labor and delivery: No established use (8.2)
- Nursing mothers: Not recommended (8.3)
- Pediatric use: Safety and effectiveness have not been established (8.4)
- Geriatric use: Reduced dose in elderly to decrease side effects (8.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

{04/07}

010680-01

ZOLPIDEM TARTRATE TABLETS
I 04/07

010680-01

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Zolpidem tartrate tablets are indicated for the short-term treatment of insomnia characterized by difficulties with sleep initiation. Zolpidem tartrate tablets have been shown to decrease sleep latency for up to 35 days in controlled clinical studies *[see Clinical Studies (14)]*.

The clinical trials performed in support of efficacy were 4-5 weeks in duration with the final formal assessments of sleep latency performed at the end of treatment.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage in adults
The dose of zolpidem tartrate tablets should be individualized.
The recommended dose for adults is 10 mg immediately before bedtime.

2.2 Special Populations
Elderly or debilitated patients may be especially sensitive to the effects of zolpidem tartrate tablets. Patients with hepatic insufficiency do not clear the drug as rapidly as normals. An initial 5 mg dose is recommended in these patients *[see Warnings and Precautions (5)]*.

2.3 Administration with CNS depressants:
Downward dosage adjustment may be necessary when zolpidem tartrate tablets are administered with agents having known CNS-depressant effects because of the potentially additive effects *[see Warnings and Precautions (5)]*.

2.4 Maximum daily dose:
The total zolpidem tartrate tablet dose should not exceed 10 mg per day.

3 DOSAGE FORMS AND STRENGTHS

Zolpidem tartrate tablets are available in 5 mg and 10 mg strength tablets for oral administration.

Zolpidem tartrate tablets 5 mg are round, biconvex, pink, film coated, with "par" debossed on one side and "680" on the other side. The 10 mg tablets are round, biconvex, white, film coated, with "par" debossed on one side and "681" on the other side. Tablets are not scored.

4 CONTRAINDICATIONS

4.1 Hypersensitivity
Zolpidem tartrate tablets are contraindicated in patients with known hypersensitivity to zolpidem tartrate or to any of the inactive ingredients in the formulation.

5 WARNINGS AND PRECAUTIONS

5.1 General
Because 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 that 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 zolpidem tartrate tablets. Because some of the important adverse effects of zolpidem tartrate tablets appear to be dose related *[see Dosage and Administration (2)]*, it is important to use the smallest possible effective dose, especially in the elderly.

5.2 Severe anaphylactic and anaphylactoid reactions
Rare cases of angioedema involving the tongue, glottis or larynx have been reported in patients after taking the first or subsequent doses of sedative-hypnotics, including zolpidem tartrate tablets. Some patients have had additional symptoms such as dyspnea, throat closing or nausea and vomiting that suggest anaphylaxis. Some patients have required medical therapy in the emergency department. If angioedema involves the throat, glottis or larynx, airway obstruction may occur and be fatal. Patients who develop angioedema after treatment with zolpidem tartrate tablets should not be rechallenged with the drug.

5.3 Abnormal Thinking and Behavioral Changes
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. Visual and auditory hallucinations have been reported as well as behavioral changes such as bizarre behavior, agitation and depersonalization. In controlled trials, <1% of adults with insomnia who received zolpidem reported hallucinations. In a clinical trial, 7.4 % of pediatric patients with insomnia associated with attention-deficit/hyperactivity disorder (ADHD), who received zolpidem reported hallucinations.

Complex behaviors such as "sleep-driving" (i.e., driving while not fully awake after ingestion of a sedative-hypnotic, with amnesia for the event) have been reported. These events can occur in sedative-hypnotic-naive as well as in sedative-hypnotic-experienced persons. Although behaviors such as "sleep-driving" may occur with zolpidem tartrate tablets alone at therapeutic doses, the use of alcohol and other CNS depressants with zolpidem tartrate tablets appears to increase the risk of such behaviors, as does the use of zolpidem tartrate tablets at doses exceeding the maximum recommended dose. Due to the risk to the patient and the community, discontinuation of zolpidem tartrate tablets should be strongly considered for patients who report a "sleep-driving" episode. Other complex behaviors (e.g., preparing and eating food, making phone calls, or having sex) have been reported in patients who are not fully awake after taking a sedative-hypnotic. As with "sleep-driving", patients usually do not remember these events. Amnesia, anxiety and other neuro-psychiatric 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 is drug induced, spontaneous in origin, or a result of an underlying psychiatric or physical disorder. Nonetheless, the emergence of any new behavioral sign or symptom of concern requires careful and immediate evaluation.

5.4 Withdrawal effects
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 (9)]*.

5.5 CNS depressant effects
Zolpidem tartrate tablets, like other sedative/hypnotic drugs, have CNS-depressant effects. Due to the rapid onset of action, zolpidem tartrate tablets 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 zolpidem tartrate tablets. Zolpidem tartrate tablets 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 zolpidem tartrate tablets are administered with such agents because of the potentially additive effects.

5.6 Special Populations
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 zolpidem tartrate tablets dosage is 5 mg in such patients *[see Dosage and Administration (2)]* to decrease the possibility of side effects. These patients should be closely monitored.

Use in patients with concomitant illness: Clinical experience with zolpidem tartrate tablets in patients with concomitant systemic illness is limited. Caution is advisable in using zolpidem tartrate tablets in patients with diseases or conditions that could affect metabolism or hemodynamic responses. Although studies did not reveal respiratory depressant effects at hypnotic doses of zolpidem tartrate tablets in normals or in patients with mild to moderate chronic obstructive pulmonary disease (COPD), a reduction in the Total Arousal Index together with a reduction in lowest oxygen saturation and increase in the times of oxygen desaturation below 80% and 90% was observed in patients with mild-to-moderate sleep apnea when treated with zolpidem tartrate tablets (10 mg) when compared to placebo. However, precautions should be observed if zolpidem tartrate tablets are prescribed to patients with compromised respiratory function, since sedative/hypnotics have the capacity to depress respiratory drive. Post-marketing reports of respiratory insufficiency, most of which involved patients with pre-existing respiratory impairment, have been received. Data in end-stage renal failure patients repeatedly treated with zolpidem tartrate tablets 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 (12.3)]*. 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, zolpidem tartrate tablets 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 over-dosage 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.

Pediatric patients: Safety and effectiveness of zolpidem has not been established in pediatric patients. In an 8-week study in pediatric patients (aged 6-17 years) with insomnia associated with ADHD, zolpidem did not decrease sleep latency compared to placebo. Hallucinations were reported in 7.4% of the pediatric patients who received zolpidem; none of the pediatric patients who received placebo reported hallucinations *[see Use in Specific Populations: Pediatric Use (8.4)]*.

5.7 Laboratory tests
Monitoring: There are no specific laboratory tests recommended to monitor zolpidem levels.

Interference with laboratory tests: Zolpidem is not known to interfere with commonly employed clinical laboratory tests. In addition, clinical data indicate that zolpidem does not cross-react with benzodiazepines, opiates, barbiturates, cocaine, cannabinoids, or amphetamines in two standard urine drug screens.

6 ADVERSE REACTIONS

Serious adverse reactions including severe anaphylactic and anaphylactoid reactions, abnormal thinking and behavior, complex behaviors, withdrawal effects, amnesia, anxiety, other neuro-psychiatric symptoms and CNS-depressant effects have been reported with zolpidem *[see Warnings and Precautions (5)]*.

6.1 Incidence in controlled clinical trials

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 U.S. trials were daytime drowsiness (0.5%), dizziness (0.4%), headache (0.5%), nausea (0.6%), and vomiting (0.5%).

Approximately 4% of 1,959 patients who received zolpidem at all doses (1 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 (1.1%), dizziness/vertigo (0.8%), amnesia (0.5%), nausea (0.5%), headache (0.4%), and falls (0.4%).

Data from a clinical study in which selective serotonin reuptake inhibitor- (SSRI) treated patients were given zolpidem revealed that four of the seven discontinuations during double-blind treatment with zolpidem (n=95) were associated with impaired concentration, continuing or aggravated depression, and manic reaction; one patient treated with placebo (n =97) was discontinued after an attempted suicide.

Most commonly observed adverse events in controlled trials: During short-term treatment (up to 10 nights) with zolpidem tartrate tablets 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 to 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 events observed at an incidence of ≥1% in controlled trials: The following tables enumerate treatment-emergent adverse event frequencies that were observed at an incidence equal to 1% or greater among patients with insomnia who received zolpidem tartrate tablets 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 patient 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 zolpidem patients are included.

The following table was derived from a pool of three placebo-controlled long-term efficacy trials involving zolpidem tartrate tablets. These trials involved patients with chronic insomnia who were treated for 28 to 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/ 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	-
Lightheadedness	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 zolpidem.

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.

Adverse event incidence across the entire preapproval database: zolpidem tartrate tablets were administered to 3,660 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 3,660 individuals exposed to zolpidem, at all doses, 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 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 zolpidem tartrate tablets, they were not necessarily caused by it.

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, syncope. Rare: abnormal accommodation, altered saliva, flushing, glaucoma, hypotension, impotence, increased saliva, tenesmus.

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

Cardiovascular system: Infrequent: cerebrovascular disorder, hypertension, tachycardia. Rare: angina pectoris, 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, illusion, leg cramps, migraine, paresthesia, sleeping (after daytime dosing), speech disorder, stupor, tremor. Rare: abnormal gait, abnormal thinking, aggressive reaction, apathy, appetite increased, decreased libido, delusion, dementia, depersonalization, dysphasia, feeling strange, hypokinesia, hypotonia, hysteria, intoxicated feeling, manic reaction, neuralgia, neuritis, neuropathy, neurosis, panic attacks, paresis, personality disorder, somnambulism, suicide attempts, tetany, yawning.

Gastrointestinal system: Frequent: hiccup. Infrequent: constipation, dysphagia, flatulence, gastroenteritis. Rare: enteritis, eructation, esophagospasm, gastritis, hemorrhoids, intestinal obstruction, rectal hemorrhage, tooth caries.

Hematologic and lymphatic system: Rare: anemia, hyperhemoglo-binemia, leukopenia, lymphadenopathy, macrocytic anemia, purpura, thrombosis.

Immunologic system: Rare: abscess herpes simplex herpes zoster, otitis externa, otitis media.

Liver and biliary system: Infrequent: abnormal hepatic function, increased SGPT. Rare: bilirubinemia, increased SGOT.

Metabolic and nutritional: Infrequent: hyperglycemia, thirst. Rare: gout, hypercholesteremia, hyperlipidemia, increased alkaline phosphatase, increased BUN, periorbital edema.

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: Infrequent: pruritus. Rare: acne, bullous eruption, dermatitis, furunculosis, injection-site inflammation, photosensitivity reaction, urticaria.

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

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

7 DRUG INTERACTIONS

7.1 CNS-active drugs
Zolpidem tartrate tablets were 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 *[see Warnings and Precautions: CNS depressant effects (5.5)]*.

A single-dose interaction study with zolpidem 10 mg and fluoxetine 20 mg at steady-state levels in male volunteers did not demonstrate any clinically significant pharmacokinetic or pharmacodynamic interactions. When multiple doses of zolpidem and fluoxetine at steady-state concentrations were evaluated in healthy females, the only significant change was a 17% increase in the zolpidem half-life. There was no evidence of an additive effect in psychomotor performance.

Following five consecutive nightly doses of zolpidem 10 mg in the presence of sertraline 50 mg (17 consecutive daily doses, at 7:00 am, in healthy female volunteers), zolpidem C_{max} was significantly higher (43%) and T_{max} was significantly decreased (53%). Pharmacokinetics of sertraline and N-desmethylsertraline were unaffected by zolpidem.

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

7.2 Drugs that affect drug metabolism via cytochrome P450
A randomized, double-blind, crossover interaction study in ten healthy volunteers between itraconazole (200 mg once daily for 4 days) and a single dose of zolpidem (10 mg) given 5 hours after the last dose of itraconazole resulted in a 34% increase in $AUC_{0-\infty}$. There were no significant pharmacodynamic effects of zolpidem on subjective drowsiness, postural sway, or psychomotor performance.

A randomized, placebo-controlled, crossover interaction study in eight healthy female volunteers between 5 consecutive daily doses of rifampin (600 mg) and a single dose of zolpidem (20 mg) given 17 hours after the last dose of rifampin showed significant reductions of the AUC (–73%), C_{max} (–58%), and $T_{1/2}$ (–36%) of zolpidem together with significant reductions in the pharmacodynamic effects of zolpidem.

7.3 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic effects: Pregnancy Category C

Zolpidem tartrate was administered to pregnant Sprague-Dawley rats by oral gavage during the period of organogenesis at doses of 4, 20, or 100 mg based/kg/day. Adverse maternal and embryo/fetal effects occurred at doses of 20 mg base/kg and higher, manifesting as dose-related lethargy and ataxia in pregnant rats while examination of fetal skull bones revealed a dose-related trend toward incomplete ossification. Teratogenicity was not observed at any dose level. The no-effect dose of zolpidem for maternal and embryofetal toxicity was 4 mg base/kg/day (between 4 to 5 times the MRHD of zolpidem tartrate tablets on a mg/m^2 basis).

Administration of zolpidem tartrate to pregnant Himalayan Albino rabbits at doses of 1, 4, or 16 mg base/kg/day by oral gavage (over 35 times the MRHD of zolpidem tartrate tablets on a mg/m^2 basis) during the period of organogenesis produced dose-related maternal sedation and decreased maternal body weight gain at all doses. At the high dose of 16 mg base/kg, there was an increase in postimplantation fetal loss and under-ossification of sternebrae in viable fetuses. Teratogenicity was not observed at any dose level. The no-effect dose of zolpidem for maternal toxicity was below 1 mg base/kg/day (< 2-times the MRHD of zolpidem tartrate tablets on a mg/m^2 basis). The no-effect dose for embryofetal toxicity was 4 mg base/kg/day (between 9 and 10 times the MRHD of zolpidem tartrate tablets on a mg/m^2 basis).

Administration of zolpidem tartrate at doses of 4, 20, or 100 mg base/kg/day to pregnant Sprague-Dawley rats starting on Day 15 of gestation and continuing through Day 21 of the postnatal lactation period produced dose-dependent lethargy and ataxia in dams at doses of 20 mg base/kg and higher. Decreased maternal body weight gain as well as evidence on non-secreting mammary glands and a single incidence of maternal death was observed at 100 mg base/kg. Effects observed on rat pups included decreased body weight with maternal doses of 20 mg base/kg and higher and decreased pup survival at maternal doses of 100 mg base/kg. The no-effect dose for maternal and offspring toxicity was 4 mg base/kg (between 4 to 5 times the MRHD of zolpidem tartrate tablets on a mg/m^2 basis).

There are no adequate and well-controlled studies in pregnant women. Zolpidem tartrate tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic 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.

8.2 Labor and delivery
Zolpidem tartrate tablets have no established use in labor and delivery.

8.3 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 hr). 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 zolpidem tartrate tablets in nursing mothers is not recommended.

8.4 Pediatric use
Safety and effectiveness of zolpidem have not been established in pediatric patients.

In an 8-week controlled study, 201 pediatric patients (aged 6-17 years) with insomnia associated with attention-deficit/hyperactivity disorder (90% of the patients were using psychoanaleptics), were treated with an oral solution of zolpidem, 0.25 mg/kg/day, up to a maximum of 10 mg/day (n=136), or placebo (n = 65). Zolpidem did not significantly decrease latency to persistent sleep, compared to placebo, as measured by polysomnography after 4 weeks of treatment. Psychiatric and nervous system disorders comprised the most frequent (> 5%) treatment emergent adverse events observed with zolpidem versus placebo and included dizziness (23.5% vs. 1.5%), headache (12.5% vs. 9.2%), and hallucinations (7.4% vs. 0%) *[see Warnings and Precautions: Special Populations (5.6)]*. Ten patients on zolpidem (7.4%) discontinued treatment due to an adverse event.

8.5 Geriatric use

A total of 154 patients in U.S. controlled clinical trials and 897 patients in non-U.S. clinical trials who received zolpidem were ≥60 years of age. For a pool of U.S. patients receiving zolpidem at doses of ≤10 mg or placebo, there were three adverse events occurring at an incidence of at least 3% for zolpidem and for which the zolpidem incidence was at least twice the placebo incidence (i.e., they could be considered drug related).

Adverse Event	Zolpidem	Placebo
Dizziness	3%	0%
Drowsiness	5%	2%
Diarrhea	3%	1%

A total of 30/1,959 (1.5%) non-U.S. patients receiving zolpidem reported falls, including 28/30 (93%) who were ≥70 years of age. Of these 28 patients, 23 (82%) were receiving zolpidem doses >10 mg. A total of 24/1,959 (1.2%) non-U.S. patients receiving zolpidem reported confusion, including 18/24 (75%) who were ≥70 years of age. Of these 18 patients, 14 (78%) were receiving zolpidem doses >10 mg.

The recommended dose of zolpidem tartrate tablets is 5 mg in elderly to decrease the possibility of side effects *[see Dosage and Administration (2) and Warnings and Precautions (5)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled substance
Zolpidem tartrate is classified as a Schedule IV controlled substance by federal regulation.

9.2 Abuse
Abuse and addiction are separate and distinct from physical dependence and tolerance. Abuse is characterized by misuse of the drug for non-medical purposes, often in combination with other psychoactive substances. Physical dependence is a state of adaptation that is manifested by a specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist. Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug effects over time. Tolerance may occur to both desired and undesired effects of drugs and may develop at different rates for different effects.

Addiction is a primary, chronic, neurobiological disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving. Drug addiction is a treatable disease, using a multidisciplinary approach, but relapse is common.

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

9.3 Dependence
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 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 dependence during treatment at recommended doses. Rare post-marketing reports of abuse, dependence and withdrawal have been received.

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

10 OVERDOSAGE

10.1 Signs and symptoms
In European postmarketing 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.

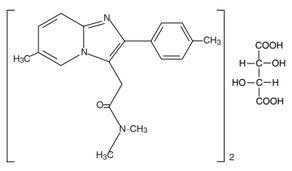
10.2 Recommended treatment
General symptomatic and supportive measures should be used along with immediate gastric lavage where appropriate. Intravenous fluids should be administered as needed. Flumazenil may be useful. As in all cases of drug overdose, respiration, pulse, blood pressure, and other appropriate 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.

11 DESCRIPTION

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-tolylimidazo[1,2-a] pyridine-3-acetamide L-(+)-tartrate (2:1). It has the following structure:



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 zolpidem tartrate tablet includes the following inactive ingredients: hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinized starch and titanium dioxide; the 5 mg tablet also contains iron oxide black, iron oxide red, iron oxide yellow, and triacetin; the 10 mg tablet also contains polyethylene glycol 400 and polysorbate 80.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of action
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 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 a 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 omega receptor subtypes, zolpidem *in vitro* binds the (ω_1) receptor preferentially with a high affinity ratio of the $alpha_1$/$alpha_5$ subunits. The (ω_1) receptor is found primarily on the Lamina IV of the sensorimotor cortical regions, substantia nigra (parsreticulata), 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 (stages 3 and 4) in human studies of zolpidem at hypnotic doses.

12.3 Pharmacokinetics
The pharmacokinetic profile of zolpidem tartrate tablets is characterized by rapid absorption from the GI tract and a short elimination half-life ($T_{1/2}$) 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 to 113) and 121 (range: 58 to 272) ng/mL, respectively, occurring at a mean time (T_{max}) of 1.6 hours for both. The mean zolpidem tartrate tablets elimination half-life was 2.6 (range: 1.4 to 4.5) and 2.5 (range: 1.4 to 3.8) hours, for the 5 and 10 mg tablets, respectively. Zolpidem tartrate tablets are converted to inactive metabolites that are eliminated primarily by renal excretion. Zolpidem tartrate tablets 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 zolpidem tartrate tablets 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 2.2hr). The half-life remained unchanged. These results suggest that, for faster sleep onset, zolpidem tartrate tablets should not be administered with or immediately after a meal.

In the elderly, the dose for zolpidem tartrate tablets should be 5 mg *[see Warnings and Precautions (5) and Dosage and Administration (2)]*. This recommendation is based on several studies in which the mean C_{max}, $T_{1/2}$, and AUC were significantly increased when compared to results in young adults. In one study of eight elderly subjects (>70 years), the means for C_{max}, $T_{1/2}$, 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 to 40 years) following a single 20 mg oral dose. Zolpidem tartrate tablets do not accumulate in elderly subjects following nightly oral dosing of 10 mg for 1 week.

The pharmacokinetics of zolpidem tartrate tablets 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 two times (250 vs 499 ng/mL) and five times (788 vs 4,203 ng·hr/mL) higher, respectively, in hepatically compromised patients. T_{max} did not change. The mean half-life in cirrhotic patients of 9.9 hr (range: 4.1 to 25.8 hr) was greater than that observed in normals of 2.2 hr (range: 1.6 to 2.4 hr). Dosing should be modified accordingly in patients with hepatic insufficiency *[see Warnings and Precautions (5) and Dosage and Administration (2)]*.

The pharmacokinetics of zolpidem tartrate were studied in 11 patients with end-stage renal failure (mean Cl_{Cr} = 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 concentration adjustments were made. On day 1, C_{max} was 172 ± 29 ng/mL (range: 46 to 344 ng/mL). After repeated dosing for 14 or 21 days, C_{max} was 203 ± 32 ng/mL (range: 28 to 316 ng/mL). On day 1, T_{max} was 1.7 ± 0.3 hr (range: 0.5 to 3.0 hr); after repeated dosing T_{max} was 0.8 ± 0.2 hr (range: 0.5 to 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, $T_{1/2}$ was 2.4 ± 0.4 hr (range: 0.4 to 5.1 hr). After repeated dosing, $T_{1/2}$ was 2.5 ± 0.4 hr (range: 0.7 to 4.2 hr). AUC was 796 ± 159 ng·hr/mL after the first dose and 818 ± 170 ng·hr/mL after repeated dosing. Zolpidem was not hemodialyzable. No accumulation of unchanged drug appeared after 14 or 21 days. Zolpidem tartrate tablet 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: 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 impairment 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, including half-lives of active metabolites, are short, drug and metabolites will be cleared before the next dose is ingested, and carryover effects related to excessive sedation or CNS depression should be minimal or absent. Zolpidem tartrate tablets have 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 zolpidem tartrate tablets.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, mutagenesis, impairment of fertility
Carcinogenesis: Zolpidem was administered to rats and mice for 2 years at dietary dosages of 4, 18, and 80 mg/kg/day. In mice, these doses are 26 to 520 times or 2 to 35 times the maximum 10 mg human dose on a mg/kg or mg/m^2 basis, respectively. In rats these doses are 43 to 876 times or 6 to 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 to 100 mg base/kg or 5 to 130 times the recommended human dose in mg/m^2. No effects on any other fertility parameters were noted.

14 CLINICAL STUDIES

14.1 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 two 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.

Normal elderly adults (mean age 68) experiencing transient insomnia (n = 35) during the first two nights in a sleep laboratory were evaluated in a double-blind, crossover, 2-night trial comparing four doses of zolpidem (5, 10, 15 and 20 mg) and placebo. All zolpidem doses were superior to placebo on the two primary PSG parameters (sleep latency and efficiency) and all four subjective outcome measures (sleep duration, sleep latency, number of awakenings, and sleep quality).

14.2 Chronic insomnia
Zolpidem was evaluated in two controlled studies for the treatment of patients with chronic insomnia (most closely resembling primary insomnia, as defined in the APA Diagnostic and Statistical Manual of Mental Disorders, DSM-IV™). Adult outpatients with chronic insomnia (n = 75) were evaluated in a double-blind, parallel group, 5-week trial comparing two 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.

Adult outpatients (n=141) with chronic insomnia were also evaluated, in a double-blind, parallel group, 4-week trial comparing two 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 treatment week. Zolpidem 15 mg was superior to placebo on a subjective measure of total 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.

14.3 Studies Pertinent To Safety Concerns For Sedative/Hypnotic Drugs
Next-day residual effects: Next-day residual effects of zolpidem tartrate tablets were evaluated in seven studies involving normal volunteers. In three studies in adults (including one study in a phase advance model of transient insomnia) and in one study in elderly subjects, a small but statistically significant decrease in performance was observed in the Digit Symbol Substitution Test (DSST) when compared to placebo. Studies of zolpidem tartrate tablets in non-elderly patients with insomnia did not detect evidence of next-day residual effects using the DSST, the Multiple Sleep Latency Test (MSLT), and patient ratings of alertness.

Rebound effects: There was no objective (polysomnographic) evidence of rebound insomnia at recommended doses seen in studies evaluating sleep on the nights following discontinuation of zolpidem tartrate tablets. 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: Controlled studies in adults utilizing objective measures of memory yielded no consistent evidence of next-day memory impairment following the administration of zolpidem tartrate tablets. However, in one study involving zolpidem doses of 10 and 20 mg, there was a significant decrease in next-morning recall of information presented to subjects during peak drug effect (90 minutes post-dose), i.e., these subjects experienced anterograde amnesia. There was also subjective evidence from adverse event data for anterograde amnesia occurring in association with the administration of zolpidem tartrate tablets, predominantly at doses above 10 mg.

Effects on sleep stages: In studies that measured the percentage of sleep time spent in each sleep stage, zolpidem tartrate tablets have generally been shown to preserve sleep stages. Sleep time spent in stages 3 and 4 (deep sleep) was found comparable to placebo with only inconsistent, minor changes in REM (paradoxical) sleep at the recommended dose.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied
Zolpidem Tartrate Tablets 5 mg are round, biconvex, pink, film coated, with "par" debossed on one side and "680" on the other side. They are supplied as follows:

NDC Number	Size
49884-680-01	bottle of 100 tablets
49884-680-10	bottle of 1000 tablets

Zolpidem Tartrate Tablets 10 mg are round, biconvex, white, film coated, with "par" debossed on one side and "681" on the other side. They are supplied as follows:

NDC Number	Size
49884-681-01	bottle of 100 tablets
49884-681-10	bottle of 1000 tablets

16.2 Storage and handling
Store at controlled room temperature 20°–25° C (68°–77°F).

17 PATIENT COUNSELING INFORMATION

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

17.2 FDA-approved patient labeling
Your doctor has prescribed zolpidem tartrate tablets 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 zolpidem tartrate tablets, be sure to ask your doctor or pharmacist.

Zolpidem tartrate tablets are used to treat different types of sleep problems in adults, 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

Zolpidem tartrate tablets belong 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. Daytime drowsiness is best avoided by taking the lowest dose possible that will still help you sleep at night. Your doctor will work with you to find the dose of zolpidem tartrate tablets that is best for you.

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

- When you first start taking zolpidem tartrate tablets 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 zolpidem tartrate tablets or any sleep medicine. Alcohol can increase the side effects of zolpidem tartrate tablets 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 zolpidem tartrate tablets.
- Always take the exact dose of zolpidem tartrate tablets 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.

"Sleep-Driving" and other complex behaviors: There have been reports of people getting out of bed after taking a sleep medicine and driving their cars while not fully awake, often with no memory of the event. If you experience such an event, it should be reported to your doctor immediately, since "sleep-driving" can be dangerous. This behavior is more likely to occur when zolpidem tartrate tablets are taken with alcohol or other drugs such as those for the treatment of depression or anxiety. Other behaviors such as preparing and eating food, making phone calls, or having sex have been reported in people who are not fully awake after taking a sleep medicine. As with "sleep-driving", people usually do not remember these events.

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 sleep 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 zolpidem tartrate tablets. In most instances memory problems can be avoided if you take zolpidem tartrate tablets 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 zolpidem tartrate tablets or any sleep medicine.

Withdrawal: Withdrawal symptoms may occur when sleep medicines are stopped suddenly after being used daily 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 1 or 2 nights.

If you have been taking zolpidem tartrate tablets 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 zolpidem tartrate tablets 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 zolpidem tartrate tablets.

Children: Zolpidem tartrate tablets have not been shown to help children fall asleep. Hallucinations, headache and dizziness have all been reported as side effects in children who were given zolpidem tartrate tablets.

SAFE USE OF SLEEPING MEDICINES

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

1. Zolpidem tartrate tablet 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 zolpidem tartrate tablets.
2. Never use zolpidem tartrate tablets or any other sleep medicine for longer than directed by your doctor.
3. If you develop an allergic reaction such as a rash, hives, shortness of breath, or swelling of your tongue or throat when using zolpidem tartrate tablets or any other sleep medicine, discontinue zolpidem tartrate tablets or other sleep medicine immediately and contact your doctor.
4. If you notice any unusual and/or disturbing thoughts or behavior during treatment with zolpidem tartrate tablets or any other sleep medicine, contact your doctor.
5. 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 zolpidem tartrate tablets or any other sleep medicine.
6. Do not take zolpidem tartrate tablets unless you are able to get a full night's sleep before you must be active again. For example, zolpidem tartrate tablets should not be taken on an overnight airplane flight of less than 7 to 8 hours since "traveler's amnesia" may occur.
7. Do not increase the prescribed dose of zolpidem tartrate tablets or any other sleep medicine unless instructed by your doctor.
8. When you first start taking zolpidem tartrate tablets 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.
9. Be aware that you may have more sleeping problems the first night or two after stopping zolpidem tartrate tablets or any other sleep medicine.
10. Be sure to tell your doctor if you are pregnant, if you are planning to become pregnant, or if you become pregnant while taking zolpidem tartrate tablets.
11. As with all prescription medicines, never share zolpidem tartrate tablets or any other sleep medicine with anyone else. Always store zolpidem tartrate tablets or any other sleep medicine in the original container out of reach of children.
12. Zolpidem tartrate tablets work very quickly. You should only take zolpidem tartrate tablets right before going to bed and are ready to go to sleep.

Manufactured by
PAR PHARMACEUTICAL COMPANIES, INC.
Spring Valley, NY 10977

Issued: 04/07 OS680-01-1-01

NDC 49884-680-01

Zolpidem Tartrate Tablets C IV

5 mg

Rx only

100 Tablets

PAR PHARMACEUTICAL

Each tablet contains:
Zolpidem Tartrate ..... 5 mg

USUAL DOSAGE:
One or two tablets at bedtime as directed.
See accompanying product literature.

KEEP THIS AND ALL DRUGS OUT OF REACH OF CHILDREN.

Pharmacist: Dispense in a tight, light-resistant, child-resistant container as defined in the USP.

Store at 20° to 25°C (68° to 77°F) excursions permitted between 15° to 30°C (59° to 86°F). [See USP Controlled Room Temperature].

Control No.:

Exp. Date:

I04/06 LA680-01-1-01

Par Pharmaceutical Companies, Inc.
Spring Valley, NY 10977

N 49884-680-01 5

NDC 49884-680-10

Zolpidem Tartrate Tablets C IV

5 mg

Rx only

1000 Tablets

PAR PHARMACEUTICAL

Each tablet contains:
Zolpidem Tartrate ..... 5 mg

USUAL DOSAGE:
One or two tablets at bedtime as directed.
See accompanying product literature.

KEEP THIS AND ALL DRUGS OUT OF REACH OF CHILDREN.

Pharmacist: Dispense in a tight, light-resistant, child-resistant container as defined in the USP.

Store at 20° to 25°C (68° to 77°F) excursions permitted between 15° to 30°C (59° to 86°F). [See USP Controlled Room Temperature].

Control No.: LA680-10-1-01

Exp. Date: I04/06

Par Pharmaceutical Companies, Inc.
Spring Valley, NY 10977

N 3 49884-680-10 7

NDC 49884-681-01

Zolpidem Tartrate Tablets C IV

10 mg

Rx only

100 Tablets

PAR PHARMACEUTICAL

Each tablet contains:
Zolpidem Tartrate ..... 10 mg

USUAL DOSAGE:
One tablet at bedtime as directed.
See accompanying product literature.

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Pharmacist: Dispense in a tight, light-resistant, child-resistant container as defined in the USP.

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Control No.:

Exp. Date:

I04/06

LA681-01-1-01

Par Pharmaceutical Companies, Inc.
Spring Valley, NY 10977

3 49884-681-01 2

NDC 49884-681-10

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Control No.:

Exp. Date:

I04/06

LA681-10-1-01

Par Pharmaceutical Companies, Inc.
Spring Valley, NY 10977

N 3 49884-681-10 4

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-062

LABELING REVIEWS

FIRST GENERIC

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-062

Date of Submission: December 22, 2000 (Original Submission)

Applicant's Name: Par Pharmaceutical, Inc.

Established Name: Zolpidem Tartrate Tablets, 5 mg and 10 mg

Labeling Deficiencies:

1. CONTAINER (Bottles of 100s and 1000s)

   a. Enhance the prominence of the controlled substance symbol by increasing its size and setting it apart from the established name. Refer to 21 CFR 1302 for guidance.

   b. To be in compliance with 21 CFR 1302.06, please ensure that a tamper evident seal is affixed to the closure of each container.

   c. Please ensure that the established name and strength of the drug appear as the most prominent information on the label, i.e., decrease the size of "Par".

2. INSERT

   a. TITLE - Enhance the prominence of the controlled substance symbol.

   b. PRECAUTIONS

      i. Drug Interactions (Drugs that affect drug metabolism via cytochrome P450) - Revise so that the "$0 \Rightarrow \infty$" appears as a subscript to "AUC" in the first sentence of the first paragraph.

      ii. Carcinogenesis, Mutagenesis, Impairment of Fertility (Mutagenesis) - Correct the spelling of "rat".

3. INFORMATION FOR PATIENTS TAKING ZOLPIDEM TARTRATE TABLETS

   a. GENERAL COMMENT: We note that INFORMATION FOR PATIENTS TAKING ZOLPIDEM TARTRATE TABLETS only appears at the end of the package insert. We also note that there is no notification to the pharmacist regarding its existence or instruction on how this information is to be distributed. Since this information alerts patients to potential side effects of this drug product, discusses special concerns of those using zolpidem, and gives tips on how to use it safely, please explain how this information is to be distributed to the patient. Include explanations for the 100 as well as the 1000 tablet package sizes.

   b. SIDE EFFECTS - "Lightheadedness" should appear as the third bullet.

Please revise your labels and labeling, as instructed above, and submit four draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please

be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other factors (print size, prominence, etc.) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes -

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Wm. Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 24		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	

Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

NOTES/QUESTIONS TO THE CHEMIST: None

FOR THE RECORD:

1. MODEL LABELING - This review is based on the labeling of AMBIEN® by Lorex Pharmaceuticals, NDA 19-908/S-009; revised December 13, 1999; approved December 1, 1999; acknowledged and retained August 2, 2000.

   I noted that there is a section entitled INFORMATION FOR PATIENTS TAKING ZOLPIDEM TARTRATE TABLETS at the end of the package insert of the innovator's labeling that provides a significant amount of information for the patient. However, there is no instruction for the information to be torn off and given to the patient. I telephoned ——— ——— to find out if patient information sheets accompanied the bottles of Ambien and was told that only one package insert was attached to the lid of the bottle. Believing this to be an oversight on the innovator's part, and believing that this information is important enough that the patient should have access to it, I've asked Par to comment on how it plans to distribute this information to the patient. Since the innovator does not provide separate sheets, we probably cannot require the generics to do so. But I believe it is at least worthy of an inquiry.

   This is the first generic for this drug product.

2. PATENTS AND EXCLUSIVITIES

Patent Data For NDA 19-908

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4382938	October 21, 2006	U-74	Method of providing hypnotic effect	P-III	None

Exclusivity Data For NDA 19-908

Code/sup	Expiration	Use Code	Description		Labeling Impact
			There are no unexpired exclusivities		None

3. MANUFACTURING FACILITY (Vol. A1.8, Section IX, Page 3977)

   Par Pharmaceuticals
   One Ram Ridge Road
   Spring Valley, NY 10977

4. STORAGE CONDITIONS:
   NDA - Store at controlled room temperature, 20° - 25°C (68° - 77°F)
   ANDA - Store at controlled room temperature, 20° - 25°C (68° - 77°F)
   USP - Not a USP item

5. DISPENSING RECOMMENDATIONS:
   NDA -Pharmacist: Dispense in a tight, light resistant, child-resistant container
   ANDA - Pharmacist: Dispense in a tight, light resistant, child-resistant container as defined in the USP
   USP - Not applicable

6. SCORING:
   NDA - unscored
   ANDA -unscored

7. PRODUCT LINE:
   The innovator markets its product in bottles of 100 and unit dose cartons of 100.

   The applicant proposes to market its product in bottles of 100 and 1000.

8. CONTAINER/CLOSURE SYSTEM: (Vol. A1.9, Section XIII, Page 4531-32)

   CONTAINER: 60 cc or 200 cc ——— white opaque, wide mouth, round bottle consisting of ——— ——— resin and ——— White — colorant

   CLOSURE: ——— 33 mm child-resistant, push down and turn, plastic metal cap for the 60 cc bottle
   45 mm knurled, flat top, metal screw cap for the 200 cc bottle

9. PRODUCT DESCRIPTION:

   The tablet debossing(s) have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95). The tablets are described as follows:

   5 mg tablets: Round, biconvex, pink, film coated, with "par" debossed on one side and "680" on the other side.

   10 mg tablets: Round, biconvex, white, film coated, with "par" debossed on one side and "681" on the other side.

10. INACTIVE INGREDIENTS:
    The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 3667 (Volume A1.9, Section VII).

11. BIOEQUIVALENCE: The Division of Bioequivalence concluded on March 28, 2001 that the firm's fasting, food, and dissolution studies were acceptable.

Date of Review:	Date of Submission:
July 5, 2001	December 22, 2000 (Original Submission)

Primary Reviewer: Date:
[signature] 7/10/01
Team Leader: Date:
Debra M. Catterson for/ 7/10/01

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cc: ANDA: 76-062
DUP/DIVISION FILE
HFD-613/LGolson/JGrace (no cc)
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Review

APPROVAL SUMMARY

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-062

Date of Submission: August 23, 2001 (Amendment)

Applicant's Name: Par Pharmaceutical, Inc.

Established Name: Zolpidem Tartrate Tablets, 5 mg and 10 mg

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? Yes.

CONTAINER LABELS:

(100s and 1000s) - Satisfactory as of August 23, 2001 submission (Vol. A3.1, Attachments II, III and IV).

PATIENT PACKAGE INSERT LABELING (Code #010680-01):

Satisfactory as of August 23, 2001 submission (Vol. A3.1, Attachments II, III, and IV)

PATIENT INFORMATION SHEET (Issued 08/01):

Satisfactory as of August 23, 2001 submission (Vol. A3.1, Attachments II, III, and IV)

BASIS OF APPROVAL:

Patent Data For NDA 19-908

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4382938	October 21, 2006	U-74	Method of providing hypnotic effect	P-III	None

Exclusivity Data For NDA 19-908

Code/sup	Expiration	Use Code	Description		Labeling Impact
			There are no unexpired exclusivities		None

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Ambien Tablets

NDA Number: 19-908

NDA Drug Name: Zolpidem Tartrate Tablets

NDA Firm: Lorex Pharmaceuticals

Date of Approval of NDA Insert and supplements #009: December 1, 1999

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: Side-by-side comparison with RLD labeling

Other comments: None

NOTES/QUESTIONS TO THE CHEMIST: None

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 24		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	

Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
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Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD:

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Patent Data For NDA 19-908

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4382938	October 21, 2006	U-74	Method of providing hypnotic effect	P-III	None

Exclusivity Data For NDA 19-908

Code/sup	Expiration	Use Code	Description		Labeling Impact
			There are no unexpired exclusivities		None

3. MANUFACTURING FACILITY (Vol. A1.8, Section IX, Page 3977)

Par Pharmaceuticals
One Ram Ridge Road
Spring Valley, NY 10977

4. STORAGE CONDITIONS:
NDA - Store at controlled room temperature, 20° - 25°C (68° - 77°F)
ANDA - Store at controlled room temperature, 20° - 25°C (68° - 77°F)
USP - Not a USP item

5. DISPENSING RECOMMENDATIONS:
NDA -Pharmacist: Dispense in a tight, light resistant, child-resistant container
ANDA - Pharmacist: Dispense in a tight, light resistant, child-resistant container as defined in the USP
USP - Not applicable

6. SCORING:
NDA - unscored
ANDA -unscored

7. PRODUCT LINE:
The innovator markets its product in bottles of 100 and unit dose cartons of 100.
The applicant proposes to market its product in bottles of 100 and 1000.

8. CONTAINER/CLOSURE SYSTEM: (Vol. A1.9, Section XIII, Page 4531-32)

CONTAINER: 60 cc or 200 cc ———, white opaque, wide mouth, round bottle consisting of ——— ——— resin and——— White — colorant

CLOSURE: ——— 33 mm child-resistant, push down and turn, plastic metal cap for the 60 cc bottle
45 mm knurled, flat top, metal screw cap for the 200 cc bottle

9. PRODUCT DESCRIPTION:

The tablet debossing(s) have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95). The tablets are described as follows:

5 mg tablets: Round, biconvex, pink, film coated, with "par" debossed on one side and "680" on the other side.

10 mg tablets: Round, biconvex, white, film coated, with "par" debossed on one side and "681" on the other side.

10. INACTIVE INGREDIENTS:
The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 3667 (Volume A1.9, Section VII).

11. BIOEQUIVALENCE: The Division of Bioequivalence concluded on March 28, 2001 that the firm's fasting, food, and dissolution studies were acceptable.

Date of Review:
January 10, 2002

Date of Submission:
August 23, 2001 (Amendment)

Primary Reviewer:
L.O. Golson

Date:
1/10/02

Team Leader:
John J Grace

Date:
1/14/2002

cc: ANDA: 76-062
DIVISION FILE
HFD-613/LGolson/JGrace (no cc)
V:\FIRMSNZ\PAR\LTRS&REV\76062ap.l
Review

APPEARS THIS WAY
ON ORIGINAL

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-062

Date of Submission: August 28, 2006 (Amendment)

Applicant's Name: Par Pharmaceutical, Inc.

Established Name: Zolpidem Tartrate Tablets, 5 mg and 10 mg

Labeling Deficiencies:

1. CONTAINER (Bottles of 100s and 1000s)
   5 mg only: Revise the "USUAL DOSAGE" statement to read "One or two tablets at bedtime..." to be in accord with the RLD. Please resubmit the 10 mg container labels since the 5 mg and 10 mg container labels were submitted in the same PDF file in the August 28, 2006 submission.

2. INSERT
   Satisfactory in final print as of the August 28, 2006 electronic submission.

3. PATIENT INFORMATION SHEET
   Satisfactory in final print as of the August 23, 2001 submission. However, we encourage you to submit this electronically.

Please revise your container labels as described above and submit either electronically or in hard copy. However, for ease of review, we recommend that you submit them electronically.

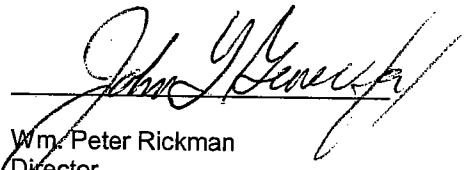
The electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format. For additional information, please refer to 21 CFR 314.94(d)(ii), SPL Implementation Guide for FDA Content of Labeling Submissions at http://www.fda.gov/cder/regulatory/ersr/SPL2aIG_v20051006_r1.pdf and Docket 92S-0251, Memorandum 32.

Although Docket 92S-0251, Memorandum 32 states that as of October 31, 2005, Structured Product Labeling (SPL) in XML format is the only acceptable format for the submission of the content of labeling in electronic format, abbreviated new drug applications not listed as the referenced listed drug (RLD) may be submitted in PDF and MS Word until the SPL for the RLD is posted on the DailyMed website at http://dailymed.nlm.nih.gov/dailymed/about.cfm. Should you decide to take the option of waiting until the SPL for the RLD is posted on the website, you will be responsible for submitting your content of labeling in SPL within 30 days after the SPL for the RLD is posted on the DailyMed website. If you have any questions on SPL submissions, please call Mr. Koung Lee at 301-827-7336.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.



Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

NOTES/QUESTIONS TO THE CHEMIST: None

Lillie Golson preformed the initial review

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 29		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the		X	

unprotected conditions of use of referenced by the RLD?			
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD:

1. MODEL LABELING - This review is based on the labeling of AMBIEN® by Lorex Pharmaceuticals, NDA 19-908/S-009; revised December 13, 1999; approved December 1, 1999; acknowledged and retained August 2, 2000.

   I noted that there is a section entitled INFORMATION FOR PATIENTS TAKING ZOLPIDEM TARTRATE TABLETS at the end of the package insert of the innovator's labeling that provides a significant amount of information for the patient. However, there is no instruction for the information to be torn off and given to the patient. I telephoned ———————— to find out if patient information sheets accompanied the bottles of Ambien and was told that only one package insert was attached to the lid of the bottle. Believing this to be an oversight on the innovator's part, and believing that this information is important enough that the patient should have access to it, I've asked Par to comment on how it plans to distribute this information to the patient. Since the innovator does not provide separate sheets, we probably cannot require the generics to do so. But I believe it is at least worthy of an inquiry.

   This is the first generic for this drug product.

2. PATENTS AND EXCLUSIVITIES

Patent Data For NDA 19-908

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4382938	October 21, 2006	U-74	Method of providing hypnotic effect	P-III	None

Exclusivity Data For NDA 19-908

Code/sup	Expiration	Use Code	Description		Labeling Impact
			There are no unexpired exclusivities		None

3. MANUFACTURING FACILITY (Vol. A1.8, Section IX, Page 3977)

   Par Pharmaceuticals
   One Ram Ridge Road
   Spring Valley, NY 10977

4. STORAGE CONDITIONS:
   NDA - Store at controlled room temperature, 20° - 25°C (68° - 77°F)
   ANDA - Store at controlled room temperature, 20° - 25°C (68° - 77°F)
   USP - Not a USP item

5. DISPENSING RECOMMENDATIONS:
   NDA -Pharmacist: Dispense in a tight, light resistant, child-resistant container
   ANDA - Pharmacist: Dispense in a tight, light resistant, child-resistant container as defined in the USP
   USP - Not applicable

6. SCORING:
   NDA - unscored
   ANDA -unscored

7. PRODUCT LINE:
   The innovator markets its product in bottles of 100 and unit dose cartons of 100.

The applicant proposes to market its product in bottles of 100 and 1000.

8. CONTAINER/CLOSURE SYSTEM: (Vol. A1.9, Section XIII, Page 4531-32)

CONTAINER: 60 cc or 200 cc ——— white opaque, wide mouth, round bottle consisting of ——— ——— resin and——— White — colorant

CLOSURE: ——— 33 mm child-resistant, push down and turn, plastic metal cap for the 60 cc bottle
45 mm knurled, flat top, metal screw cap for the 200 cc bottle

9. PRODUCT DESCRIPTION:

The tablet debossing(s) have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95). The tablets are described as follows:

5 mg tablets: Round, biconvex, pink, film coated, with "par" debossed on one side and "680" on the other side.

10 mg tablets: Round, biconvex, white, film coated, with "par" debossed on one side and "681" on the other side.

10. INACTIVE INGREDIENTS:
The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 3667 (Volume A1.9, Section VII).

11. BIOEQUIVALENCE: The Division of Bioequivalence concluded on March 28, 2001 that the firm's fasting, food, and dissolution studies were acceptable.

Date of Review: September 6, 2006 Date of Submission: August 28, 2006

Primary Reviewer: Ruby Wu Date: 9/6/06

Team Leader: John Grace Date: 9-6-06

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cc: ANDA: 76-062
DIVISION FILE
HFD-613/RWu/JGrace (no cc)
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Review

APPROVAL SUMMARY

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-062

Date of Submission: September 13, 2006 and October 3, 2006 (Amendments)

Applicant's Name: Par Pharmaceutical, Inc.

Established Name: Zolpidem Tartrate Tablets, 5 mg and 10 mg

APPROVAL SUMMARY

Do you have Final Printed Labels and Labeling? Yes.

1. CONTAINER (Bottles of 100s and 1000s)
   Satisfactory in final print as of the September 13, 2006 electronic submission.

2. COMBINED PHYSICIAN INSERT AND PATIENT INFORMATION SHEET
   Satisfactory in final print as of the August 28, 2006 electronic submission.

3. PATIENT INFORMATION SHEET
   Satisfactory as of August 23, 2001 submission (Vol. A3.1, Attachments II, III, and IV)

Revisions needed post-approval: Yes. The following are requested insert labeling revisions from my review of your amendment dated September 13, 2006 for ANDA 76-062 for Par Pharmaceutical, Inc. The revisions are "POST-APPROVAL" revisions and may be submitted in an annual report, provided the changes are described in full.

Patient information leaflet:
Third paragraph, second sentence: "There are many different..."
Special Concerns, first sentence: "...problems that may occur while..."

BASIS OF APPROVAL:

Patent Data For NDA 19-908

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4382938	October 21, 2006	U-74	Method of providing hypnotic effect	P-III	None

Exclusivity Data For NDA 19-908

Code/sup	Expiration	Use Code	Description		Labeling Impact
			There are no unexpired exclusivities		None

Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Ambien Tablets
NDA Number: 19-908
NDA Drug Name: Zolpidem Tartrate Tablets
NDA Firm: Sanofi Aventis
Date of Approval of NDA Insert and supplements #009: December 1, 1999
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: Side-by-side comparison with RLD labeling

NOTES/QUESTIONS TO THE CHEMIST: None

Lillie Golson preformed the initial review

FOR THE RECORD:

1. MODEL LABELING - This review is based on the labeling of AMBIEN® by Sanofi Aventis, NDA 19-908/S-009; revised December 13, 1999; approved December 1, 1999; acknowledged and retained August 2, 2000.

   I noted that there is a section entitled INFORMATION FOR PATIENTS TAKING ZOLPIDEM TARTRATE TABLETS at the end of the package insert of the innovator's labeling that provides a significant amount of information for the patient. However, there is no instruction for the information to be torn off and given to the patient. I telephoned ——— to find out if patient information sheets accompanied the bottles of Ambien and was told that only one package insert was attached to the lid of the bottle. Believing this to be an oversight on the innovator's part, and believing that this information is important enough that the patient should have access to it, I've asked Par to comment on how it plans to distribute this information to the patient. Since the innovator does not provide separate sheets, we probably cannot require the generics to do so. But I believe it is at least worthy of an inquiry.

2. PATENTS AND EXCLUSIVITIES

Patent Data For NDA 19-908

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4382938	October 21, 2006	U-74	Method of providing hypnotic effect	P-III	None

Exclusivity Data For NDA 19-908

Code/sup	Expiration	Use Code	Description		Labeling Impact
			There are no unexpired exclusivities		None

3. MANUFACTURING FACILITY (Vol. A1.8, Section IX, Page 3977)

   Par Pharmaceuticals
   One Ram Ridge Road
   Spring Valley, NY 10977

4. STORAGE CONDITIONS:
   NDA - Store at controlled room temperature, 20° - 25°C (68° - 77°F)
   ANDA - Store at controlled room temperature, 20° - 25°C (68° - 77°F)
   USP - Not a USP item

5. DISPENSING RECOMMENDATIONS:
   NDA -Pharmacist: Dispense in a tight, light resistant, child-resistant container
   ANDA - Pharmacist: Dispense in a tight, light resistant, child-resistant container as defined in the USP
   USP - Not applicable

6. SCORING:
   NDA - unscored
   ANDA -unscored

7. PRODUCT LINE:
   The innovator markets its product in bottles of 100 and unit dose cartons of 100.
   The applicant proposes to market its product in bottles of 100 and 1000.

8. CONTAINER/CLOSURE SYSTEM: (Vol. A1.9, Section XIII, Page 4531-32)

   CONTAINER: 60 cc or 200 cc ——— white opaque, wide mouth, round bottle consisting of ———
   ——— resin and ——— White ——colorant

CLOSURE: ——— 33 mm child-resistant, push down and turn, plastic metal cap for the 60 cc bottle
45 mm knurled, flat top, metal screw cap for the 200 cc bottle

9. PRODUCT DESCRIPTION:

The tablet debossing(s) have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95). The tablets are described as follows:

5 mg tablets: Round, biconvex, pink, film coated, with "par" debossed on one side and "680" on the other side.

10 mg tablets: Round, biconvex, white, film coated, with "par" debossed on one side and "681" on the other side.

10. INACTIVE INGREDIENTS:
The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 3667 (Volume A1.9, Section VII).

11. BIOEQUIVALENCE: The Division of Bioequivalence concluded on March 28, 2001 that the firm's fasting, food, and dissolution studies were acceptable.

12. SPL:
The firm has tried submitting SPL in 2 separate submission but error has been found in both submissions. We will not hold-up the approval of an ANDA due to SPL. Therefore, we will ask the firm to submit the SPL post-approval. I spoke to Julie Szozda of Par on 10/17/06 @ 10:25 am. She will continue to work with the SPL group in correcting their submission.

From: ———
Sent: *Tuesday, October 17, 2006 8:56 AM*
To: *Wu, Ruby (Chi-Ann)*
Subject: *RE: please load...*
On ANDA 76062, this is the same error as last time they submitted SPL. If they are not going to change the SPL we will not be able to upload it. They have to contact SPL@FDA.HHS.GOV to find out how to fix the SPL.

———
Consultant, CDER/OBPS
SPL Support

Date of Review: October 17, 2006 Date of Submission: September 13, 2006 and October 3, 2006

Primary Reviewer: Ruby Wu Date:

Team Leader: John Grace Date:

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Review

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

/s/

Ruby Wu
10/17/2006 11:16:19 AM
MEDICAL OFFICER

John Grace
10/17/2006 03:33:56 PM
MEDICAL OFFICER

***This review supersedes the review signed off on 10/17/06 **

APPROVAL SUMMARY

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-062

Date of Submission: April 18, 2007 (Amendment)

Applicant's Name: Par Pharmaceutical, Inc.

Established Name: Zolpidem Tartrate Tablets, 5 mg and 10 mg

APPROVAL SUMMARY

Do you have Final Printed Labels and Labeling? Yes.

1. CONTAINER (Bottles of 100s and 1000s)
   Satisfactory in final print as of the April 18, 2007 electronic submission.

2. COMBINED PHYSICIAN INSERT AND PATIENT INFORMATION SHEET
   Satisfactory in final print as of the April 18, 2007 electronic submission.

Revisions needed post-approval: No.

BASIS OF APPROVAL:

Patent Data For NDA 19-908

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4382938/*PED	October 21, 2006/ April 21, 2007	U-74	Method of providing hypnotic effect	P-III	None

Exclusivity Data For NDA 19-908

Code/sup	Expiration	Use Code	Description	Labeling Impact
S-022	MAR 29,2010	M-54	INFORMATION FROM PEDIATRIC STUDIES ADDED TO LABEL	None: Based on BPCA consult, all negative pediatric info was deemed "safety or risk associated" and should be kept in the labeling
S-022	SEP 29,2010	PED	PEDIATRIC EXCLUSIVITY	

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Ambien Tablets

NDA Number: 19-908

NDA Drug Name: Zolpidem Tartrate Tablets

NDA Firm: sanofi-aventis, U.S. Inc.

Date of Approval of NDA Insert and supplements: NDA 19-908/S-022; approved March 28, 2007

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: Side-by-side comparison with RLD labeling

NOTES/QUESTIONS TO THE CHEMIST: None

Lillie Golson preformed the initial review

FOR THE RECORD:

1. MODEL LABELING - This review is based on the labeling of AMBIEN® Tablets by sanofi-aventis, U.S. Inc., NDA 19-908/S-022; approved March 28, 2007.

   This supplemental new drug application provides for labeling to reflect that zolpidem did not decrease sleep latency compared to placebo in an 8-week study of pediatric patients and to describe psychiatric and central nervous system adverse events, including hallucinations. Ambien® was awarded three years of Waxman-Hatch exclusivity, which expires on March 29, 2010, based upon the sponsor's pediatric clinical study performed in response to the zolpidem written request. In addition, the sponsor was awarded pediatric exclusivity for the zolpidem moiety, resulting in six additional months protection for every zolpidem product by Sanofi Aventis US with patent protection or exclusivity. The additional protection for this product expires April 21, 2007 and September 29, 2010 respectively.

   A Best Pharmaceuticals for Children Act (BPCA) consult was submitted. On April 16, 2007, a t-con was held with all 4 disciplines. Conclusion: all of the negative pediatric info was deemed "safety or risk associated" and should be kept in the labeling of generic products. The following representatives participated in the t-con:

   Office of Pediatric Drug Development and Program Initiatives:
   - Pica-Branco, Denise
   - Sachs, Hari

   Division of Neurology Products:
   - McNeil, D Elizabeth
   - Michaloski, Cathleen

   Study Endpoints and Label Development (SEALD) Team
   - Rosario, Lilliam
   - Furness, Melissa

   OCC
   - Dettelbach, Kim

   Drug substance and drug product not subject to USP monograph (checked USP 29 and USP 30 on April 16, 2007)

   I noted that there is a section entitled INFORMATION FOR PATIENTS TAKING ZOLPIDEM TARTRATE TABLETS at the end of the package insert of the innovator's labeling that provides a significant amount of information for the patient. However, there is no instruction for the information to be torn off and given to the patient. I telephoned [redacted] to find out if patient information sheets accompanied the bottles of Ambien and was told that only one package insert was attached to the lid of the bottle. Believing this to be an oversight on the innovator's part, and believing that this information is important enough that the patient should have access to it, I've asked Par to comment on how it plans to distribute this information to the patient. Since the innovator does not provide separate sheets, we probably cannot require the generics to do so. But I believe it is at least worthy of an inquiry.

   On April 20, 2007, I spoke to Julie Szozda of Par. Julie said she believes Par does provide stand-alone patient information leaflets. Julie will provide this post approval.

2. PATENTS AND EXCLUSIVITIES

Patent Data For NDA 19-908

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4382938/*PED	October 21, 2006/ April 21, 2007	U-74	Method of providing hypnotic effect	P-III	None

Exclusivity Data For NDA 19-908

Code/sup	Expiration	Use Code	Description	Labeling Impact
S-022	MAR 29,2010	M-54	INFORMATION FROM PEDIATRIC STUDIES ADDED TO LABEL	None: Based on BPCA consult, all negative pediatric info was deemed "safety or risk associated" and should be kept in

				the labeling

3. MANUFACTURING FACILITY (Vol. A1.8, Section IX, Page 3977)

   Par Pharmaceuticals
   One Ram Ridge Road
   Spring Valley, NY 10977

4. STORAGE CONDITIONS:
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   ANDA - Pharmacist: Dispense in a tight, light resistant, child-resistant container as defined in the USP
   USP - Not applicable

6. SCORING:
   NDA - unscored
   ANDA -unscored

7. PRODUCT LINE:
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   The applicant proposes to market its product in bottles of 100 and 1000.

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   CONTAINER: 60 cc or 200 cc ——— white opaque, wide mouth, round bottle consisting of ——— resin and ——— White — colorant

   CLOSURE: ——— 33 mm child-resistant, push down and turn, plastic metal cap for the 60 cc bottle
   45 mm knurled, flat top, metal screw cap for the 200 cc bottle

9. PRODUCT DESCRIPTION:

   The tablet debossing(s) have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95). The tablets are described as follows:

   5 mg tablets: Round, biconvex, pink, film coated, with "par" debossed on one side and "680" on the other side.

   10 mg tablets: Round, biconvex, white, film coated, with "par" debossed on one side and "681" on the other side.

10. INACTIVE INGREDIENTS:
    The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 3667 (Volume A1.9, Section VII).

11. BIOEQUIVALENCE: The Division of Bioequivalence concluded on March 28, 2001 that the firm's fasting, food, and dissolution studies were acceptable.

Date of Review: April 20, 2007 Date of Submission: April 18, 2007

Primary Reviewer: Ruby Wu

Team Leader: John Grace

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

/s/

Ruby Wu
4/20/2007 03:09:51 PM
MEDICAL OFFICER

John Grace
4/20/2007 10:44:10 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-062

CHEMISTRY REVIEWS

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Abbreviated New Drug Application Review

---

1. CHEMISTRY REVIEW NO.: 1

2. ANDA #: 76-062

3. NAME AND ADDRESS OF APPLICANT:
Par Pharmaceutical, Inc.
One Ram Ridge Road
Spring Valley, NY 10977

4. LEGAL BASIS FOR SUBMISSION:
Reference-Listed Drug: Ambien®
Lorex-Pharmaceuticals
Application No. N19908
Strength: Zolpidem Tartrate Tablets, 5 and 10 mg

Paragraph III certification: U.S. Patent No. 4,382,938 expires on October 21, 2006 (Use code: U-74, method of providing hypnotic effect).

Exclusivity: None

5. SUPPLEMENT(s): N/A

6. PROPRIETARY NAME: None

7. NONPROPRIETARY NAME:
Zolpidem Tartrate

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

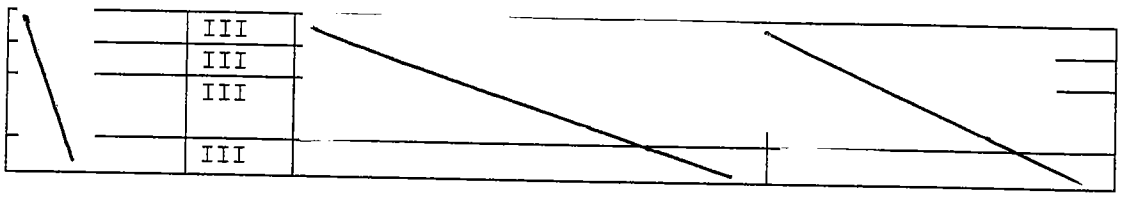
9. AMENDMENTS AND OTHER DATES:
22-DEC-2000 Date of ANDA submission.

10. PHARMACOLOGICAL CATEGORY: Short term treatment of insomnia.

11. Rx or OTC: Rx

12. RELATED IND/NDA/DMF(s):

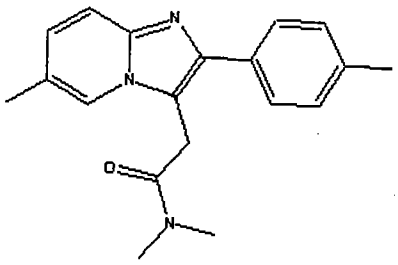
DMF#	TYPE	SUBJECT	HOLDER
	II		
	IV		
	IV		
	III		
	III		
	IV		
	IV		
	III		



13. DOSAGE FORM: Tablets

14. POTENCIES: 5 mg & 10 mg

15. CHEMICAL NAME AND STRUCTURE:
N,N,6-Trimethyl-2-p-tolylimidazol[1,2-α]pyridine-3-acetamide L-(+)-tartrate (2:1)



$C_{42}H_{48}N_6O_8$ or $(C_{19}H_{21}N_3O)_2 \cdot C_4H_6O_6$ mol.wt. 765

Zolpidem ($C_{19}H_{21}N_3O$)

16. RECORDS AND REPORTS: None

17. COMMENTS:
-Review comments are described in the review item No. 38.

-The following sections are not satisfactory:
- 23. Raw material controls
- 26. Container
- 28. Laboratory controls
- 29. Stability

-The following sections are pending:
- 32. Labeling
- 33. EER

-Both the drug substance and drug products are not USP articles. Method validation for drug substance and products were sent to Northeast Regional Laboratory (HFR-NE500) on 29-MAY-2001.

18. CONCLUSIONS AND RECOMMENDATIONS:
The application is not approvable (Minor).

19. REVIEWER: Gil Kang

DATE COMPLETED: 25-MAY-2001
Corrected: 04-JUN-2001

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confidential commercial

information from

CHEMISTRY REVIEW #1

2. Since both the drug substance and product are not USP articles, the analytical methods require validation by the FDA laboratories. Please submit samples when requested.

Sincerely yours,

M Smela for 6/5/01

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc: ANDA 76-062
ANDA 76-062/ Division File
Field Copy
Hfd-92

Endorsements:

HFD-629/G.Kang/GK 6/4/01
HFD-629/P.Schwartz, Ph.D./5/30/01/6/4/01 PS 6/4/01
HFD-617/M.Dillahunt, PM/5/31/01 MDillahunt 6/5/01
V:\FIRMSNZ\PAR\LTRS&REV\76062NA1.1RD
F/T by: DJ 5/31/01

CHEMISTRY REVIEW - Not Approvable - Minor

APPEARS THIS WAY
ON ORIGINAL

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Abbreviated New Drug Application Review

1. CHEMISTRY REVIEW NO.: 2

2. ANDA #: 76-062

3. NAME AND ADDRESS OF APPLICANT:
Par Pharmaceutical, Inc.
Attention: Janis A. Picurro
One Ram Ridge Road
Spring Valley, NY 10977

4. LEGAL BASIS FOR SUBMISSION:
Reference-Listed Drug: Ambien®
Lorex-Pharmaceuticals
Application No. N19908
Strength: Zolpidem Tartrate Tablets, 5 and 10 mg

Paragraph III certification: U.S. Patent No. 4,382,938 expires on October 21, 2006 (Use code: U-74, method of providing hypnotic effect).

Exclusivity: None

5. SUPPLEMENT(s): N/A

6. PROPRIETARY NAME: None

7. NONPROPRIETARY NAME:
Zolpidem Tartrate

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:

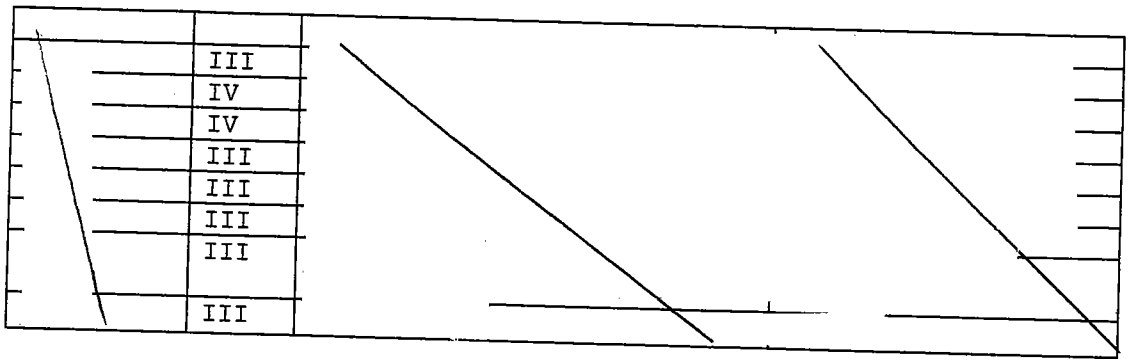
22-DEC-2000	Date of ANDA submission.
10-JUL-2001	Deficiency letter (minor)
01-AUG-2001	Response to deficiency letter
23-AUG-2001	Labeling

10. PHARMACOLOGICAL CATEGORY: Short term treatment of insomnia.

11. Rx or OTC: Rx

12. RELATED IND/NDA/DMF(s):

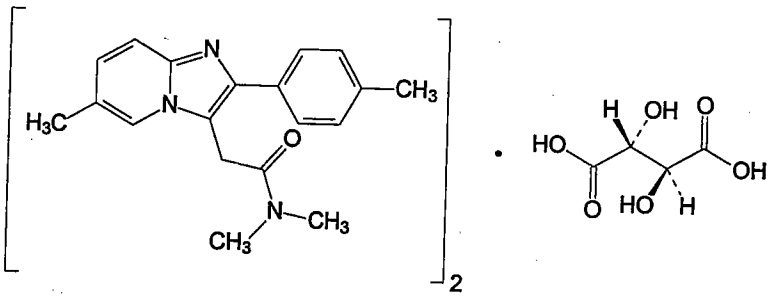
DMF#	TYPE	SUBJECT	HOLDER
	II		
	IV		
	IV		
	III		



13. DOSAGE FORM: Tablets

14. POTENCIES: 5 mg & 10 mg

15. CHEMICAL NAME AND STRUCTURE:
Bis[N,N-dimethyl-2-[6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridin-3-yl]acetamide] (2R,3R)-2,3-dihydroxybutanedioate (2:1)



$C_{42}H_{48}N_6O_8$ or $(C_{19}H_{21}N_3O)_2 \cdot C_4H_6O_6$ mol.wt. 765

16. RECORDS AND REPORTS: None

17. COMMENTS:

-The following sections are not satisfactory:
- 22. Synthesis
- 23. Raw material controls
- 28. Laboratory controls

-The following sections are pending:
- 32. Labeling
- 33. EER

-Both the drug substance and drug products are not USP articles. Method validation for drug substance and products were requested to the Northeast Regional Laboratory (HFR-NE500) on 29-MAY-2001. The result of method validation on 17-AUG-2001 memorandum indicates that the method appears to be suitable for regulatory analysis of this product with following comments:

1. The method for the impurities in the drug substance lists [redacted] for the determination. It was necessary to state in the method which [redacted].

2. The method does not require the [redacted]

-Par notes and acknowledges that the firms referenced in the application relative to the manufacturing and testing of the product must be in compliance with cGMPs at the time of approval. And also acknowledges that since both the drug substance and product are not USP articles, the analytical methods require validation by the FDA laboratories.

18. CONCLUSIONS AND RECOMMENDATIONS:
The application is not approvable (Minor).

19. REVIEWER: Gil Kang DATE COMPLETED: 24-SEP-2001

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CHEMISTRY REVIEW #2

cc: ANDA 76-062
ANDA 76-062/ Division File
DUP
Field Copy

Endorsements:

HFD-627/G.Kang/9/25/01 GK 10/10/01
HFD-629/J.Fan, Team leader/10/6/01 10/10/01
HFD-617/S.Ho, PM/10/10/01 10/11/01
V:\FIRMSNZ\PAR\LTRS&REV\76062NA1.2RD
F/T by: gp/10/10/01

CHEMISTRY REVIEW - Not Approvable - Minor

APPEARS THIS WAY
ON ORIGINAL

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Abbreviated New Drug Application Review

1. CHEMISTRY REVIEW NO.: 3

2. ANDA #: 76-062 (First generic)

3. NAME AND ADDRESS OF APPLICANT:
Par Pharmaceutical, Inc.
Attention: Janis A. Picurro
One Ram Ridge Road
Spring Valley, NY 10977

4. LEGAL BASIS FOR SUBMISSION:
Reference-Listed Drug: Ambien®
Lorex-Pharmaceuticals
Application No. N19908
Strength: Zolpidem Tartrate Tablets, 5 and 10 mg

Paragraph III certification: U.S. Patent No. 4,382,938 expires on October 21, 2006 (Use code: U-74, method of providing hypnotic effect).

Exclusivity: None

5. SUPPLEMENT(s): N/A

6. PROPRIETARY NAME: None

7. NONPROPRIETARY NAME: Zolpidem Tartrate

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:

22-DEC-2000	Date of ANDA submission.
10-JUL-2001	Deficiency letter #1 (minor)
01-AUG-2001	Response to deficiency letter
23-AUG-2001	Amendment (Labeling)
15-OCT-2001	Deficiency letter #2 (minor)
26-OCT-2001	Telephone conference
30-NOV-2001	Response to deficiency letter #2
30-JAN-2002	Telephone conference
11-FEB-2002	Telephone amendment
01-MAR-2002	Telephone conference
11-MAR-2002	Telephone amendment

10. PHARMACOLOGICAL CATEGORY: Short term treatment of insomnia.

11. Rx or OTC: Rx

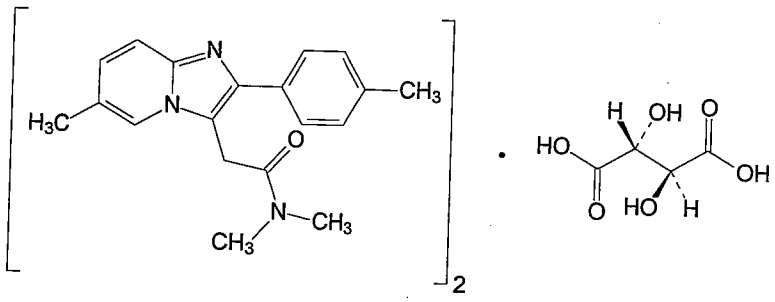
12. RELATED IND/NDA/DMF(s):

DMF#	TYPE	SUBJECT	HOLDER
	II		
	IV		
	IV		
	III		
	III		
	IV		
	IV		
	III		
	III		
	III		
	III		
	III		

13. DOSAGE FORM: Tablets

14. POTENCIES: 5 mg & 10 mg

15. CHEMICAL NAME AND STRUCTURE:
Bis[N,N-dimethyl-2-[6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridin-3-yl]acetamide] (2R,3R)-2,3-dihydroxybutanedioate (2:1) $(C_{19}H_{21}N_3O)_2 \cdot C_4H_6O_6$ mol.wt. 765



16. RECORDS AND REPORTS: None

17. COMMENTS:
Both the drug substance and drug products are not USP articles. Method validation for drug substance and products were requested to the Northeast Regional Laboratory (HFR-NE500) on 29-MAY-2001. The result of method validation (17-AUG-2001 memorandum) indicates that the method appears to be suitable for regulatory analysis of this product with comments. All deficiencies and comments are satisfactorily responded in the amendments dated 30-NOV-2001, 11-FEB-2002 and 11-MAR-2002.

18. CONCLUSIONS AND RECOMMENDATIONS:
The application is approvable.

19. REVIEWER: Gil Kang DATE COMPLETED: 12-MAR-2002

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CHEMISTRY REVIEW #3

cc: ANDA 76-062
ANDA 76-062/ Division File
DUP
Field Copy

Endorsements:

HFD-627/G.Kang/3/12/02 GK 3/13/02
HFD-629/J.Fan, Team leader/ 3/13/02

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F/T by: DJ 3/13/02

CHEMISTRY REVIEW - Approvable

APPEARS THIS WAY
ON ORIGINAL

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Abbreviated New Drug Application Review

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1. CHEMISTRY REVIEW NO.: 4

2. ANDA #: 76-062

3. NAME AND ADDRESS OF APPLICANT:
Par Pharmaceutical, Inc.
Attention: Julie Szozda
One Ram Ridge Road
Spring Valley, NY 10977

4. LEGAL BASIS FOR SUBMISSION:

Reference-Listed Drug:	Ambien® Lorex-Pharmaceuticals Application No. N19908
Strength:	Zolpidem Tartrate Tablets, 5 and 10 mg
Paragraph III certification:	U.S. Patent No. 4,382,938*PED will expire on April 21, 2007 (Use code:U-74, method of providing hypnotic effect).
Exclusivity: None	

5. SUPPLEMENT(s): N/A

6. PROPRIETARY NAME: None

7. NONPROPRIETARY NAME: Zolpidem Tartrate

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:

22-DEC-2000	Date of ANDA submission.
10-JUL-2001	Deficiency letter #1 (minor)
01-AUG-2001	Response to deficiency letter
23-AUG-2001	Amendment (Labeling)
15-OCT-2001	Deficiency letter #2 (minor)
26-OCT-2001	Telephone conference
30-NOV-2001	Response to deficiency letter #2
30-JAN-2002	Telephone conference
11-FEB-2002	Telephone amendment
01-MAR-2002	Telephone conference
11-MAR-2002	Telephone amendment
26-APR-2002	**Tentative approval**
17-MAR-2006	Amendment (the subject of this review)
16-AUG-2006	Telephone amendment (the subject of this review)
28-AUG-2006	Minor amendment (the subject of this review)

10. PHARMACOLOGICAL CATEGORY: Short term treatment of insomnia.

11. Rx or OTC: Rx

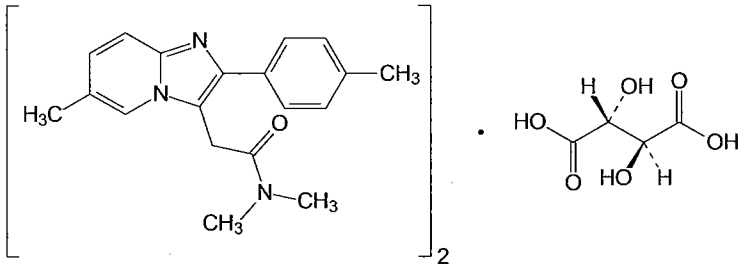
12. RELATED IND/NDA/DMF(s):

DMF#	TYPE	SUBJECT	HOLDER
	II		
	IV		
	IV		
	III		
	III		
	IV		
	IV		
	III		
	III		
	III		
	III		
	III		

13. DOSAGE FORM: Tablets

14. POTENCIES: 5 mg & 10 mg

15. CHEMICAL NAME AND STRUCTURE:
Bis[N,N-dimethyl-2-[6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridin-3-yl]acetamide] (2R,3R)-2,3-dihydroxybutanedioate (2:1) $(C_{19}H_{21}N_3O)_2 \bullet C_4H_6O_6$ mol.wt. 765



16. RECORDS AND REPORTS: None

17. COMMENTS:
-Both the drug substance and drug product are not USP articles.
-ANDA 76-062 was tentatively approved on 26-APR-2002.

Three amendments (17-MAR-2006, 16-AUG-2006 & 28-AUG-2006) are reviewed in this review cycle.

Review of the amendment dated 17-MAR-2006:
The amendment has been submitted to incorporate updates since its tentative approval. Changes are made to the in-house standard, raw material, finished product and stability

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CHEMISTRY REVIEW #4

cc: ANDA 76-062
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-630/G.Kang, Ph.D./4/18/07

HFD-630/D.Gill, Ph.D., Team Leader/4/18/07

HFD-617/L.Matheny, Project Manager/Jeanne Skanchy for 4/19/07

F/T by : LM 4/23/07

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TYPE OF LETTER: APPROVABLE

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

/s/

Gil Jong Kang
4/23/2007 05:26:12 PM
CHEMIST

Devinder Gill
4/23/2007 06:00:58 PM
CHEMIST

Leigh Matheny
4/23/2007 06:03:59 PM
CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-062

BIOEQUIVALENCE REVIEWS

Zolpidem Tartrate Tablets
5 mg and 10 mg
ANDA 76-062
Reviewer: Moheb H. Makary
W 76062SDW.D00

Par Pharmaceutical, Inc.
Spring Valley, NY

Submission Date: 12/22/00

Review of Bioequivalence Studies, Dissolution Data and a Waiver Request (Electronic Submission)

Introduction

Indication: Ambien (zolpidem tartrate) is indicated for the short-term treatment of insomnia. Ambien has been shown to decrease sleep latency and increase the duration of sleep for up to 35 days in controlled clinical studies.
Type of Submission: Electronic
Contents of Submission: Fasting and food studies on 10 mg tablet. Dissolution data on 10 mg and 5 mg tablets. Waiver request for the 5 mg strength.
RLD: Ambien^R
Recommended Dose: The dose of Ambien should be individualized. The recommended dose for adults is 10 mg immediately before bedtime.

Background

The pharmacokinetic profile of Ambien is characterized by rapid absorption from the GI tract and a short elimination half-life ($T_{1/2}$) 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 to 113) and 121 (range: 58 to 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 to 4.5) and 2.5 (range: 1.4 to 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 hr). The half-life remained unchanged. These results suggest that, for faster sleep onset, Ambien should not be administered with or immediately after a meal.

Financial Disclosure: Form FDA 3454 was submitted. The firm has no conflict of interest with the investigators.

Protocol No.: 00225, Randomized, 2-Way Crossover, Bioequivalence study of Par Pharmaceutical Inc. (USA) and G. D. Searle & Co. (USA) (Ambien^R) 10 mg Zolpidem Tartrate Tablets administered as a 1 x 10 mg Tablet in Healthy Adult Males under Fasting Conditions

Study Information

STUDY FACILITY INFORMATION
Clinical Facility: _____
Medical Director: _____
Scientific Director: _____

Clinical Study Dates:	10/05/00 to 10/19/00
Analytical Facility	———
Analytical Study Dates:	10/22/00 to 11/09/00
Storage Period:	35 Days

TREATMENT INFORMATION

Treatment ID:	A	B
Test or Reference:	T	R
Product Name:	Zolpidem tartrate	Ambien
Manufacturer:	Par Pharmaceutical Inc., USA	G. D. Searle & Co., USA
Manufacture Date:	9/5/00	N/A
Expiration Date:	N/A	3/03
ANDA Batch Size:	———	N/A
Batch/Lot Number:	27121	0C807
Potency:	99.9	97.3
Content Uniformity:	100.1	N/A
Strength:	10 mg	10 mg
Dosage Form:	tablet	tablet
Dose Administered:	10 mg	10 mg
Study Condition:	fasting	fasting
Length of Fasting:	at least 10 hours	at least 10 hours

RANDOMIZATION		DESIGN	
Randomized:	Y	**Design Type:**	crossover
No. of Sequences:	2	**Replicated Treatment Design:**	N
No. of Periods:	2	**Balanced:**	Y
No. of Treatments:	2	**Washout Period:**	7 days

DOSING		SUBJECTS	
Single or Multiple Dose:	single	**IRB Approval:**	Y
Steady State:	N	**Informed Consent Obtained:**	Y
Volume of Liquid Intake:	240 mL	**No. of Subjects Enrolled:**	26
Route of Administration:	oral	**No. of Subjects Completing:**	25
Dosing Interval:	hr	**No. of Subjects Analyzed as Per Protocol:**	24
Number of Doses:	N/A	**No. of Dropouts:**	1
Loading Dose:	N/A	**Sex(es) Included:**	male
Steady State Dose Time:	N/A	**Healthy Volunteers Only:**	Y
Length of Infusion:	N/A	**No. of Adverse Events:**	71

Dietary Restrictions: Subjects were instructed to abstain from food or beverages containing xanthine (e.g. coffee, tea, caffeine-containing sodas, colas and chocolate, etc.), grapefruit products (e.g. fresh, canned, or frozen) (See Appendix B for complete description).

Activity Restrictions: Subjects were required to remain seated for the first 4 hours after dosing avoiding complete rest. They were allowed to stand only if they needed to go to the bathroom. They were not permitted to lie down (See Appendix B for complete description).

Drug Restrictions: No concomitant drug therapy was allowed during the study except one to counteract an adverse event (e.g. occasional use of acetaminophen for headache).

Blood Sampling: Pre-dose (0 hours) and 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.25, 2.5, 3, 4, 5, 6, 8, 12 and 16 hours.

Study Results

1) Clinical
Adverse Events: Subjects were monitored for adverse events as specified in the protocol. No serious adverse events occurred during the study. A summary of adverse events is reported on page 206, Vol.1.1.

Dropouts:

SUBJECT NO.:	7
REASON:	Personal reasons
PERIOD:	2
REPLACEMENT:	N

2) Analytical (Not to be Released Under FOI)
Pre-Study Assay Validation:

ANALYTE:	ZOLPIDEM
ASSAY METHOD:	
MATRIX:	
INTERNAL STANDARD:	
SENSITIVITY:	
STANDARD CURVE HIGHEST CONC.:	
STANDARD CURVE LOWEST CONC.:	
R2 IS GREATER THAN:	
SPECIFICITY:	Y

Assay Validation

Recovery:	The mean recovery for zolpidem in human plasma was — % and —% at concentrations of — and ———, respectively.
Precision and Accuracy:	Interday and intraday precision for quality control pre-study samples ranged from — % to — % and — % to — %, respectively, for zolpidem. Interday accuracy ranged from —% to — %.
Stability:	Long Term Frozen Stability: Zolpidem was stable for a period of 57 days in human plasma at -20^{0}C. Freeze-Thaw: Zolpidem was stable after five freeze-thaw cycles in human plasma.
Precision and Accuracy:	Interday precision for quality control within-study samples ranged from —% to —% for zolpidem. Interday accuracy ranged from —% to — %.

Statistical Methods

AUCT, AUCI, CMAX, TMAX, KEL and T1/2 were calculated from the individual concentration versus time data for zolpidem. Analysis of variance was performed on each pharmacokinetic parameter using SAS GLM procedure.

Study Results

The plasma concentrations and pharmacokinetic parameters for zolpidem are summarized in Table I.

Table I

Time(hours)	Test Mean (A)	Test %CV (A)	Ref Mean (B)	Ref %CV (B)	T/R Ratio (A)/(B)
0.000	0.	0.	0.	0.	**
0.250	11.01	181.06	14.28	122.24	0.771
0.500	90.75	65.89	97.28	68.31	0.933
0.750	133.49	42.47	133.37	42.35	1.001
1.00	136.32	38.91	139.24	41.65	0.979
1.25	125.77	37.35	130.86	38.53	0.961
1.50	118.32	39.21	123.69	35.51	0.957
1.75	114.15	40.74	113.89	35.6	1.002
2.00	108.56	38.44	108.01	35.88	1.005
2.25	107.53	40.64	102.12	35.65	1.053
2.50	106.59	39.39	98.04	35.98	1.087
3.00	98.15	45.69	88.77	33.71	1.106
4.00	81.24	53.25	72.74	42.04	1.117
5.00	47.17	51.48	44.81	52.65	1.053
6.00	31.78	55.59	31.53	56.29	1.008
8.00	18.87	64.23	18.19	65.6	1.037
12.0	7.09	89.62	6.92	91.6	1.024
16.0	2.97	117.21	2.83	123.58	1.05

Mean Plasma PK Parameters

Parameter	Test Mean	Ref Mean	T/R Ratio (A)/(B) Geometric Mean
AUCT(ng.hr/mL)	616.3 (43.1)	595.5 (37.3)	1.00
AUCI(ng.hr/mL)	631.5 (44.4)	611.1 (39.0)	1.00
CMAX(ng/mL)	158.3 (35.4)	159.9 (34.8)	0.99
TMAX(hr)	1.21	1.04	
KEL(1/hr)	0.28	0.28	
THALF(hr)	2.62	2.64	

	Root MSE	90% CI
LnAUCT	0.15	93.3-108.1%
LnAUCI	0.15	93.0-108.0%
LnCMAX	0.19	89.5-108.5%

1. The mean zolpidem plasma levels peaked at 1 hour for both the test and the reference products following their administration under fasting conditions.

2. For Par's zolpidem tartrate, the mean AUCT, AUCI and CMAX values for zolpidem were 3.5%, 3.3% and 1.0% higher and lower, respectively, than those for the reference product values under fasting conditions. The 90% confidence intervals are within the acceptable range of 80-125% for log-transformed AUCT, AUCI and CMAX.

Protocol No.: 00230, Randomized, 3-Way Crossover, Bioequivalence study of Par Pharmaceutical Inc. (USA) and G. D. Searle & Co. (USA) (Ambien) 10 mg Zolpidem Tartrate Tablets administered as a 1 x 10 mg Tablet in Healthy Adult Males under Fasting and Fed Conditions

Study Information

STUDY FACILITY INFORMATION

Clinical Facility:	[redacted]
Medical Director:	
Scientific Director:	
Clinical Study Dates:	10/18/00 to 11/01/00
Analytical Facility	[redacted]
Principal Investigator:	
Analytical Study Dates:	11/03/00 to 11/18/00
Storage Period:	31 Days

TREATMENT INFORMATION

Treatment ID:	A	B	C
Test or Reference:	T	R	T
Product Name:	Zolpidem tartrate	Ambien	Zolpidem tartrate
Manufacturer:	Par Pharmaceutical Inc., USA	G. D. Searle & Co., USA	Par Pharmaceutical Inc., USA
Expiration Date:	N/A	3/03	N/A
Batch/Lot Number:	27121	0C807	27121
Strength:	10 mg	10 mg	10 mg
Dosage Form:	tablet	tablet	tablet
Dose Administered:	10 mg	10 mg	10 mg
Study Condition:	fed	fed	fasting
Length of Fasting:	N/A	N/A	at least 10 hours
Standardized Breakfast:	Y	Y	N
Breakfast Specifics:	1 buttered English muffin, 1 fried egg, 1 slice of American cheese, 1 slice of Canadian bacon, 1 serving of hash brown potatoes, 240 mL of whole milk, 180 mL of orange juice	1 buttered English muffin, 1 fried egg, 1 slice of American cheese, 1 slice of Canadian bacon, 1 serving of hash brown potatoes, 240 mL of whole milk, 180 mL of orange juice	N/A

RANDOMIZATION

Randomized:	Y
No. of Sequences:	6
No. of Periods:	3
No. of Treatments:	3

DESIGN

Design Type:	crossover
Replicated Treatment Design:	N
Balanced:	N
Washout Period:	7 days

DOSING

Single or Multiple Dose:	single
Steady State:	N
Volume of Liquid Intake:	180 mL
Route of Administration:	oral
Dosing Interval:	hr
Number of Doses:	N/A
Loading Dose:	N/A
Steady State Dose Time:	N/A
Length of Infusion:	N/A

SUBJECTS

IRB Approval:	Y
Informed Consent Obtained:	Y
No. of Subjects Enrolled:	24
No. of Subjects Completing:	23
No. of Subjects Analyzed per Protocol:	18
No. of Dropouts:	1
Sex(es) Included:	male
Healthy Volunteers Only:	Y
No. of Adverse Events:	95

Study Results

1) Clinical

Adverse Events: Most adverse events were mild or moderate in severity. One serious and severe adverse event was reported (car accident) but was judged to be unrelated to the study medication. A summary of adverse events is reported on page 1912, Vol.1.4.

Dropouts:

SUBJECT NO.:	23
REASON:	Personal reasons
PERIOD:	2
REPLACEMENT:	N

2) Analytical (Not to be Released Under FOI)

Same as the fasting study

Precision and Accuracy: Interday precision for quality control within-study samples ranged from — % to —% for zolpidem. Interday accuracy ranged from —% to —%.

Study Results

The plasma concentrations and pharmacokinetic parameters for zolpidem are summarized in Table II.

Table II

TIME (HR)	NON-FASTING TEST TREATMENT A	NON-FASTING REFERENCE TREATMENT B	FASTING TEST TREATMENT C	RATIO (A/B)	RATIO (A/C)
Pre-dose	0.00 (----)	0.00 (----)	0.00 (----)	----	----
0.333	14.32 (169.82)	12.91 (177.03)	70.18 (80.52)	1.1093	0.2040
0.667	49.38 (117.10)	40.76 (107.87)	132.62 (41.02)	1.2114	0.3723
1.00	74.39 (66.94)	68.32 (62.52)	131.39 (49.06)	1.0888	0.5662
1.25	89.54 (59.16)	87.92 (51.82)	117.73 (41.39)	1.0185	0.7606
1.50	99.44 (56.67)	96.33 (51.90)	112.79 (41.45)	1.0323	0.8816
1.75	105.29 (51.41)	99.85 (42.99)	107.92 (43.91)	1.0545	0.9756
2.00	106.60 (46.50)	99.53 (38.84)	106.35 (43.34)	1.0710	1.0023
2.25	106.69 (41.39)	99.24 (35.87)	105.62 (38.69)	1.0750	1.0101
2.50	105.43 (42.32)	93.88 (37.19)	101.60 (38.24)	1.1230	1.0377
2.75	98.15 (43.03)	89.14 (38.87)	93.80 (38.45)	1.1012	1.0464
3.00	96.71 (43.42)	85.86 (37.26)	90.91 (40.34)	1.1263	1.0638
4.00	78.10 (43.67)	70.17 (39.66)	67.56 (41.95)	1.1130	1.1560
5.00	51.78 (46.37)	46.48 (42.57)	40.30 (43.64)	1.1140	1.2847
6.00	34.26 (50.06)	30.16 (47.61)	27.37 (44.98)	1.1360	1.2516
8.00	20.23 (59.82)	16.20 (53.84)	16.20 (48.66)	1.2492	1.2487
12.0	7.53 (69.47)	6.22 (70.87)	5.76 (62.49)	1.2107	1.3068
16.0	2.75 (86.28)	2.16 (94.14)	2.00 (89.75)	1.2719	1.3721

Mean Plasma PK Parameters

Parameter	Test Mean (Fed)	Ref Mean (Fed)	Test Mean (Fasting)
AUCT	557.98 (43.2)	496.59 (39.3)	571.80 (39.3)
AUCI	570.89 (43.5)	506.94 (39.7)	582.58 (39.2)
CMAX	128.61 (40.3)	117.86 (34.7)	150.26 (42.3)
TMAX	1.71	1.69	1.06

KEL	0.309	0.311	0.316
THALF	2.47	2.41	2.46

	A/B Geometric Mean
AUCT	1.10
AUCI	1.10
CMAX	1.07

1. The zolpidem plasma levels peaked at 1.75 and 2.25 hours for the reference and the test products, respectively, under nonfasting conditions and at 0.67 hour for the test product under fasting conditions.

2. For Par's zolpidem tartrate, the mean AUC(0-t), AUCinf and Cmax values for zolpidem were 12.4%, 12.6% and 9.1% higher, respectively, than the reference product values under nonfasting conditions. The ratios of the geometric means are within the acceptable 0.8-1.25 range for AUCT, AUCI and CMAX.

3. For the test product, the mean AUC(0-t), AUCinf and Cmax values were decreased by about 2.4%, 2.0% and 14.4%, respectively, when dosed under nonfasting conditions compared to fasting conditions.

Formulations(Not to be released under FOI)

COMPARATIVE FORMULATIONS

INGREDIENT	AMOUNT (MG) PER DOSAGE UNIT STRENGTH	
	5 MG TABLET	10 MG TABLET
Zolpidem Tartrate	5.0	10.0
Lactose Monohydrate, NF		
Microcrystalline Cellulose, NF		
Pregelatinized Starch, NF		
Magnesium Stearate		

	----	---
TOTAL TABLET WEIGHT (MG)	123.6	122.4

* ———— does not appear in the final product.

Dissolution Testing

TABLE III - IN VITRO DISSOLUTION TESTING

Drug (Generic Name): Zolpidem Tartrate
Dose Strength: 5 mg and 10 mg
ANDA No.: N/A
Firm: Par Pharmaceutical, Inc.
Submission Date: December 22, 2000
File Name: PAR0102.daa (10 mg); PAR0102.dab (5 mg)

I. Conditions for Dissolution/Release Testing:

Method Ref.: In-House Method

Apparatus: 2 (paddle)	Medium: 0.01N hydrochloric acid
RPM: 50	Volume: 900 mL
No. Units Tested: 12	Tolerance :NLT —%(Q) in 30 minutes
Reference Drug: Ambien	Assay Method: HPLC

II. Results of In Vitro Dissolution/Release Testing:

Sampling Times (Min)	Test Product: Zolpidem Tartrate Tablets Lot No.: 27121 Strength: 10 mg			Reference Product: Ambien Lot No.: 0C807 Strength: 10 mg		
	Average %	Range (low-high)	% RSD	Average %	Range (low-high)	% RSD
5	76		12.3	93		4.4
10	97		1.4	100		1.0
20	97		1.4	100		1.1
30	98		1.4	101		0.8

Content Uniformity (10 units): 100.1%; % RSD 0.8; Potency Assay: Test Product Lot = 99.9%

Reference Product Lot = 97.3%

Sampling Times (Min)	Test Product: Zolpidem Tartrate Tablets Lot No.: 27120 Strength: 5 mg			Reference Product: Ambien Lot No.: 9L476 Strength: 5 mg		
	Average %	Range (low-high)	% RSD	Average %	Range (low-high)	% RSD
5	95		4.0	81		13.3
10	100		1.6	98		3.1
20	101		1.0	99		0.7
30	101		0.7	99		1.0

Content Uniformity (10 units): 101.9%; % RSD 1.4; Potency Assay: Test Product Lot = 101.5%

Reference Product Lot = 97.6%

Comments:

1. The firm's single-dose bioequivalence study #00-225 under fasting conditions, conducted on its 10 mg zolpidem tartrate tablet is acceptable. The 90% confidence intervals for LnAUC(0-t), LnAUCinf and LnCmax are within the acceptable range of 80-125% for zolpidem.

2. The firm's single-dose bioequivalence study #00-230 under fasting and nonfasting conditions, conducted on its 10 mg zolpidem tartrate tablet is acceptable. The ratios of the geometric means for zolpidem are within the acceptable 0.8-1.25 range for AUC(0-t), AUCinf and Cmax under nonfasting conditions.

3. The dissolution testing conducted by the firm on its zolpidem tartrate tablets, 10 mg and 5 mg, lot #27121 and lot #27120, respectively, is acceptable.

4. The formulation of the 5 mg strength is proportionally similar to the 10 mg strength.

Recommendations:

1. The bioequivalence studies under fasting and nonfasting conditions conducted by Par Pharmaceutical, Inc., on its Zolpidem Tartrate Tablet, 10 mg, lot #27121, comparing it to Ambien^R Tablet, 10 mg, manufactured by G.D. Searle Co., have been found acceptable by the Division of Bioequivalence. The studies demonstrate that Par's Zolpidem Tartrate Tablet, 10 mg, is bioequivalent to the reference product, Ambien^R Tablet, 10 mg, manufactured by G.D. Searle Co., under fasting and nonfasting conditions.

2. The dissolution testing conducted by the firm on its Zolpidem Tartrate Tablets, 10 mg and 5 mg, lot # 27121 and lot #27120, respectively, is acceptable. The formulation of the 5 mg strength is proportionally similar to the 10 mg strength which underwent acceptable bioequivalence testing. The waiver of *in vivo* bioequivalence study requirements for the 5 mg tablet of the test product is granted. The Division of Bioequivalence deems Zolpidem Tartrate Tablet, 5 mg, manufactured by Par Pharmaceutical, Inc., to be bioequivalent to Ambien^R Tablet, 5 mg, manufactured by G.D. Searle Co.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of 0.01N HCl at 37^{0}C using USP 24 apparatus II (paddle) at 50 rpm. The test product should meet the following specification:

> Not less than ___% (Q) of the labeled amount of the drug in dosage form is dissolved in 15 minutes.

The firm should be informed of the above recommendations.

Moheb H. Makary

Moheb H. Makary, Ph.D.
Review Branch III
Division of Bioequivalence

Date: 3/15/01

BMD 3/15/01

RD INITIALLED BDAVIT
FT INITIALLED BDAVIT Barbara Davit

Date: 3/15/01

Concur: for Dale P. Conner

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Date: 3/26/2001

Mmakary/ 3-8-01, 3-15-01, 76062sdw.D00
cc: ANDA #76-062, original, HFD-658 (Makary), Drug File, Division File.

CC: ANDA #76-062
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-658/ Reviewer M. Makary
HFD-658/ Bio team Leader B. Davit

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Printed in final on 3/15/01

Endorsements: (Final with Dates)
HFD-658/ Reviewer M. Makary
HFD-658/ Bio team Leader B. Davit 3/15/01
HFD-650/ D. Conner fw 3/28/2001

BIOEQUIVALENCY - ACCEPTABLE submission date: 12-22-00

OK 1. **FASTING STUDY** (STF) Strengths: 10 mg
Clinical: [redacted] **Outcome: AC**
Analytical: [redacted]

OK 2. **FOOD STUDY** (STF) Strengths: 10 mg
Clinical: [redacted] **Outcome: AC**
Analytical: [redacted]

OK 3. **DISSOLUTION WAIVER** (DIW) Strengths: 5 mg
Outcome: AC

Outcome Decisions: **AC** - Acceptable

FIGURE 1

PLASMA CONCENTRATIONS (ng/mL) VERSUS TIME
SINGLE-DOSE FASTING STUDY #00225

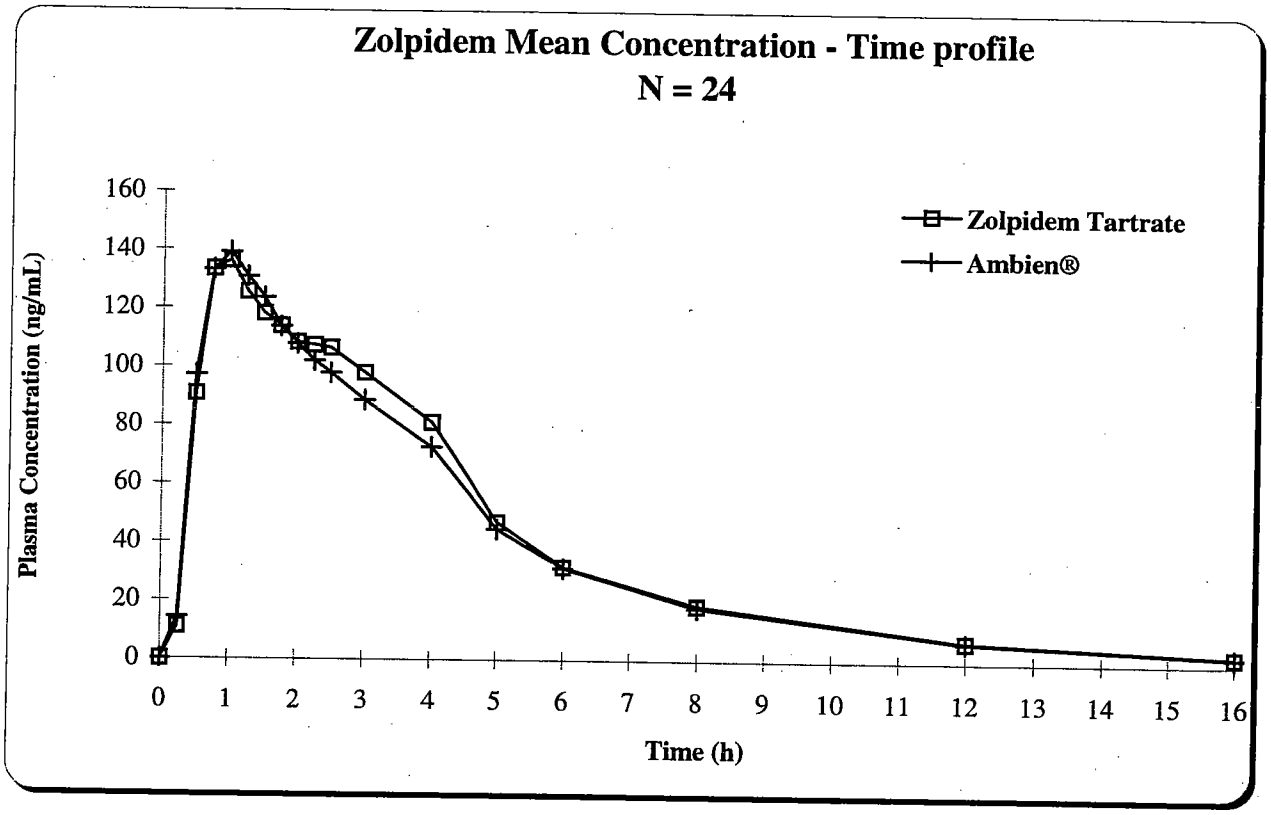
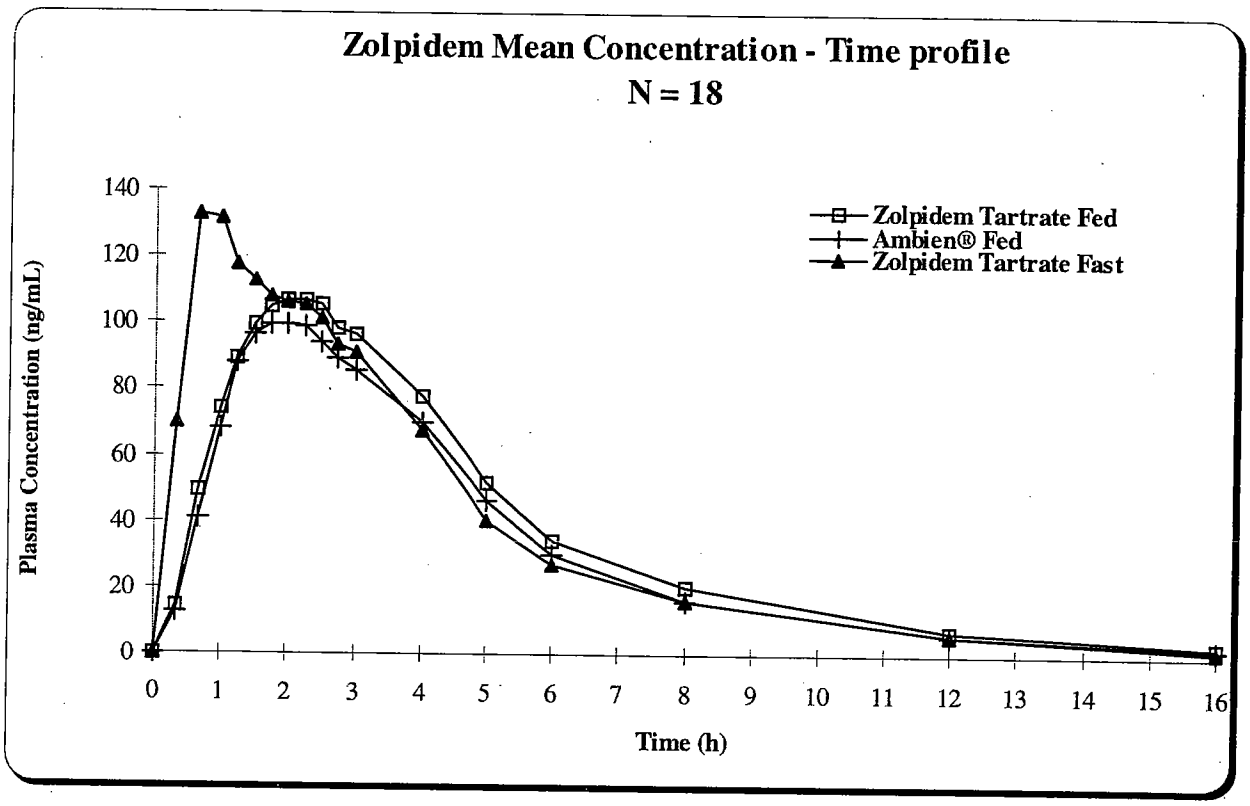


FIGURE 2

PLASMA CONCENTRATIONS (ng/mL) VERSUS TIME
SINGLE-DOSE FOOD-EFFECTS STUDY #00230



BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-062 APPLICANT: Par Pharmaceutical, Inc.

DRUG PRODUCT: Zolpidem Tartrate Tablets, 10 mg and 5 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

The following dissolution testing will need to be incorporated into your stability and quality control programs:

> The dissolution testing should be conducted in 900 mL of 0.01N HCl, at 37°C using USP Apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:
>
> Not less than —%(Q) of the labeled amount of the drug in the dosage form is dissolved in 15 minutes.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

fw Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # :76-062 SPONSOR : Par Pharmaceutical, Inc.

DRUG AND DOSAGE FORM : **Zolpidem Tartrate** Tablets

STRENGTH(S) : **10** mg and 5 mg

TYPES OF STUDIES : Two bioequivalence studies

CLINICAL STUDY SITE(S) : _____
ANALYTICAL SITE(S) _____

STUDY SUMMARY : The studies are acceptable

DISSOLUTION : Dissolution testing is acceptable. Waiver is granted for the 5 mg strength.

DSI INSPECTION STATUS

Inspection needed: YES / (NO)	Inspection status:	Inspection results:
First Generic _____	Inspection requested: (date)	
New facility _____	Inspection completed: (date)	
For cause _____		
Other _____		

PRIMARY REVIEWER : Moheb H. Makary, Ph.D. BRANCH : III

INITIAL : MHM DATE : 3/8/01

TEAM LEADER : Barbara M. Davit, Ph.D. BRANCH : III

INITIAL : BMD DATE : 3/15/01

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

for

INITIAL : Gail **DATE :** 3/26/2001

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-062

ADMINISTRATIVE DOCUMENTS

RECORD OF TELEPHONE CONVERSATION

The firm requested clarification on comment #12 of the June 5, 2001 minor deficiency.

Comment 12
Please revise the dissolution specification according to the attached bioequivalency comment as following: "Not less than —%(Q) of the labeled amount of the drug in the dosage form is dissolved in 15 minutes" Also, provide all updated long term stability data incorporating the revised specification.

The firm questioned if they should go back and test their prior stability samples with the revised specifications.

Dr. Schwartz informed the firm that they should test their 3 month retained samples with the revised specifications in addition to testing the future samples with the revised specifications.

DATE
June 15, 2001

ANDA NUMBER
76-062

IND NUMBER

TELECON

INITIATED BY

SPONSOR

X **FDA**

PRODUCT NAME
Zolpidem Tartrate Tablets, 5 mg, 10 mg

FIRM NAME
Par Pharmaceutical, Inc.

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Janice Patura

TELEPHONE NUMBER
(845) 573-5514

SIGNATURE
P. Schwartz PS 6/19/01
G. Kang GK 6/19/01
M.Dillahunt MDillahunt 6/19/01

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CC: ANDA 76-062
Chem Div I, T-con Notebook

RECORD OF TELEPHONE CONVERSATION

On this date, we contacted Par Pharmaceutical, Inc. (Par) and made reference to their ANDA 76-062, to our deficiency letter dated October 15, 2001, and to their request for a telephone conference regarding the deficiency letter.

Deficiency 3

Firm comment: Par asked if there is any particular reason why the agency wants [redacted]

FDA Response: Need to determine if the [redacted]

Deficiency 6.c

Firm comment: Is the [redacted]

FDA Response: Drug product.

Firm comment: Par would like to [redacted]

FDA Response: Par should contact the FDA Laboratory.

DATE:
10/26/01

ANDA NUMBER
76-062

TELECON INITIATED BY SPONSOR

PRODUCT NAME:
Zolpidem Tartrate Tablets, 5 mg and 10 mg

FIRM NAME:
Par Pharmaceutical, Inc.

FIRM REPRESENTATIVES:
Janise Picurro, Regulatory Affairs
M. Ragunathan, Director of Analytical R&D
Michelle Bonomi-Huvala, Senior Director of Regulatory Affairs

TELEPHONE NUMBER:
845-573-5514

FDA REPRESENTATIVES
James Fan
Gil Kang
Sarah Ho

SIGNATURES:
J.Fan 11/1/01
G.Kang 11/1/01
S.Ho 11/1/01

Orig: ANDA
Cc: Division File
Chem. I Telecon Binder
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RECORD OF TELEPHONE CONVERSATION

On this date, we contacted Par Pharmaceutical, Inc. (Par) and made reference to their ANDA 76-062 and to their minor amendment date November 30,2001. **Deficiency 2 Response** FDA comment: ——————— is not included in the test and specification for ———————. Please include as — & as test method. **Deficiency 4 Response** FDA comment: ——————————— ——— please add an additional test & specification for purity. In addition, we requested that the firm submit updated room temperature stability data. Ms. Picurro agreed to submit the above information as a telephone amendment.	**DATE:** 1/30/02 **ANDA NUMBER** 76-062 **TELECON INITIATED BY AGENT** **PRODUCT NAME:** Zolpidem Tartrate Tablets, 5 mg and 10 mg **FIRM NAME:** Par Pharmaceutical, Inc. **FIRM REPRESENTATIVES:** Janise Picurro, Regulatory Affairs **TELEPHONE NUMBER:** 845-573-5514 **FDA REPRESENTATIVES** Gil Kang Sarah Ho **SIGNATURES:** G.Kang GK 1/30/02 S.Ho 1/30/02

Orig: ANDA 84-394
Cc: Division File
Chem. I Telecon Binder
V:\FIRMSNZ\PAR\TELECONS\76062.30jan2002.doc

RECORD OF TELEPHONE CONVERSATION

On this date, we contacted Par Pharmaceutical, Inc. (Par) and made reference to their ANDA 76-062 regarding following issues. **Issue 1:** [redacted] should be tightened. This issue was discussed before with Par and considered again at approval stage. Agency decided to request to tighten the specifications. **Issue 2:** The result of [redacted] on exhibit batch was requested. If the sample from exhibit batch is not available, sample from comparable batch can be tested. **Issue 3:** [redacted] assay method for [redacted] need to be validated (esp. linearity). Agency requested that the firm respond as a telephone amendment. Ms. Picurro agreed to submit the above information as a telephone amendment.	**DATE:** 3/01/02 **ANDA NUMBER** 76-062 **TELECON INITIATED BY AGENT** **PRODUCT NAME:** Zolpidem Tartrate Tablets, 5 mg and 10 mg **FIRM NAME:** Par Pharmaceutical, Inc. **FIRM REPRESENTATIVES:** Janis Picurro, Regulatory Affairs **TELEPHONE NUMBER:** 845-573-5514 **FDA REPRESENTATIVES** Gil Kang Jim Fan Paul Schwartz **SIGNATURES:** Gil Kang 3/1/02 Jim Fan 3/1/02 Paul Schwartz 3/1/02

Orig: ANDA 76-062
Cc: Division File
Chem. I Telecon Binder
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OGD APPROVAL ROUTING SUMMARY

ANDA # 76-062
Drug: Zolpidem Tartrate Tablets

Applicant: Par Pharmaceutical, Inc.
Strength: 5 mg and 10 mg

APPROVAL ☐ TENTATIVE APPROVAL ☑ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ OTHER ☐

REVIEWER:

1. Project Manager Sarah Ho
Review Support Br 3

DRAFT RECEIPT
Date 3/25/02
Initials SH

FINAL ACTION
Date 2/27/02
Initials SH

Application Summary:

Original Rec'd date 12/26/00
Date Acceptable for Filing 12/26/00 ✓
Patent Certification (type) III
Date Patent/Exclus.expires 12/21/06
Citizens Petition/Legal Case Yes ☐ No ☑
(If YES, attach email from PM to CP coord)
First Generic Yes ☑ No ☐
(If YES, check PETS)
Pediatric Exclusivity Tracking PETS)
Date checked 2/25/02 NDA# 19908
Nothing Submitted ☐
Written request issued ☐ Request Prop. 1/28/00
Study Submitted ☐ Request not issued yet.
Previously reviewed and tentatively approved ☐ Date
Previously reviewed and CGMP def./N/A Minor issued ☐ Date
Comments:

EER Status Pending ☐ Acceptable ☑ OAI ☐
Date of EER Status 1/8/02
Date of Office Bio Review 3/26/01
Date of Labeling Approv. Sum 1/14/02
Date of Sterility Assur. App. —
Methods Val. Samples Pending Yes ☐ No ☑
30 Day Clock Start End
Commitment Rcd. from Firm Yes ☐ No ☐
Modified-release dosage form: Yes ☐ No ☑
Interim Dissol. Specs in AP Ltr: Yes ☐

2. Div. Dir./Deputy Dir.
Chemistry Div. I or II
Comments:
Telephone amendment responded to satisfactorily
mv OK

Date 2/26
Initials PJ

Date 3/14
Initials PJ

3. Frank Holcombe
Assoc. Dir. For Chemistry
Comments: (First generic drug review)
SATISFACTORY

Date
Initials

Date 4/25-/02
Initials FH

4. Pat Beers Block
Supv., Review Support Branch
EER Status: Referred to DLS see review below. JAT

Date
Initials

Date
Initials

Bioequivalence sites:
Clinical site:
Inspection needed: ☐ yes ☐ no
Status: ☐acceptable ☐unacceptable ☐ pending
Date of status:
Reason:

Analytical site:
Inspection needed: ☐ yes ☐ no
Status: ☐acceptable ☐unacceptable ☐pending
Date of status:
Reason:

Bioequivalence office level sign off:

Labeling Status:

Microbiology status:
Patent Certification:
Controlled Correspondence/Cit.Pet
Comments: RLD =

REVIEWER: **DRAFT RECEIPT** **FINAL ACTION**

5. Gregg Davis
Supv., Reg. Support Branch
Date 4/25/02 Initials [illegible] Date 4/25/02 Initials [illegible] for

Contains GDEA certification: Yes ☒ No ☐ Determ. of Involvement? Yes ☐ No ☒
(required if sub after 6/1/92)
Patent/Exclusivity Certification: Yes ☒ No ☐ Pediatric Exclusivity System
If Para. IV Certification- did applicant Notify patent holder/NDA holder Yes ☐ No ☒ Date Checked 4/25/02
Was applicant sued w/in 45 days: Yes ☐ No ☐ Nothing Submitted ☒
Has case been settled: N/A Yes ☐ No ☐ Written request issued ☒
Date settled: Study Submitted ☐
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☒
Comments: RLD=Ambien Tablets 5mg, 10mg at Lot Ex Pharmaceuticals NDA 19-908
For made a paragraph III certification to the '938 patent expiring on 12/21/06. There is no unexpired exclusivity. The division has not issued a written request for a pediatric study as of this date.

6. Peter Rickman
Acting Director, DLPS
Date 4/25/02 Initials [illegible] Date 4/25/02 Initials [illegible] for
Comments: Acceptable EES dated 1/8/02 (Verified 4/25/02). No OAI. Labels noted. Bioequivalence studies (fasting & fed on 10mg strength) found acceptable 3/5/01. Dissolution data acceptable. Waiver granted to 5mg strength. Bio studies (clinical and analytical) conducted by [redacted]. This facility has an acceptable PSI inspection history. Office level bio reviewed 3/26/01 - labeling acceptable for 4/14/02. OC acceptable 3/13/02. Methods validation completed. First generic CMC audit completed.

7. Robert L. West
Acting Deputy Director, OGD
Date 4/25/02 Initials [illegible] Date 4/25/02 Initials [illegible]

Para.IV Patent Cert: Yes ☐ No ☒; Pending Legal Action: Yes ☐ No ☒; Petition: Yes ☐ No ☒
Comments: This application is recommended for tentative approval. Final approval must await the expiration of the '938 patent (currently 10/21/06).

8. Gary Buehler
Director, OGD
Date 4/26/02 Initials GB Date 4/26/02 Initials GB
Comments:

First Generic Approval ☒ Tentative PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐

9. Project Manager Sarah Ho
Review Support Branch 3
Date 4/26/02 Initials [illegible] Date [illegible] Initials [illegible]

N/A Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
9:35 am Time notified of approval by phone 9:40 am Time approval letter faxed

FDA Notification:
4/26/02 Date e-mail message sent to "OGD approvals" account
4/26/02 Date Approval letter copied to "//cder/drugapp" directory

C:\Sarah\APROVROU.doc

FDA
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM

DATE: April 11, 2007

TO: Ruby (Chi-Ann) Wu, R.Ph., Office of Generic Drugs

THROUGH: Russell Katz, M.D., Division Director DNDP

FROM: D. Elizabeth McNeil, M.D., DNDP

RE: Proposed labeling for Ambien (zolpidem tartrate), 24 pending ANDAs

Consult Questions:

1. Are there any issues of safety or effectiveness for the remaining conditions of use when the protected pediatric information is removed from the labeling?
2. Are the proposed labeling statements acceptable?
3. Are there any statements of appropriate pediatric contraindications, warnings or precautions that should be included in the generic drug labeling?

Summary of Division Response:

As the BPCA provides for inclusion of known pediatric safety data in generic drug labeling, the label for a generic formulation of Ambien should contain all of the known efficacy/safety data for the pediatric population and therefore reproduce most of the information in the current Ambien label (approved March 2007) to adequately inform practitioners about the apparent absence of demonstrated benefit in the face of an increased risk of central nervous system (CNS) adverse effects.

Further details may be found in the table attached below.

Background:

"The Reference Listed Drug, Ambien tablets [NDA 19-908, Sanofi-Aventis US] will receive Waxman-Hatch exclusivity for miscellaneous exclusivity (M-54-Information from pediatric studies added to label) which will expire March 28, 2010. On January 4, 2002, the Best Pharmaceuticals for Children Act (BPCA) was signed into law ("Best Pharmaceuticals for Children Act" (BPCA) Section 11). The Act addresses the approval of drugs under 505(j) when pediatric information protected by exclusivity has been added to the labeling. BPCA

include section 11(a)(2) [21 USC 355a(l)(2)] amends section 505(j) of the FD&C Act to allow approval of an ANDA that omits a pediatric indication or other aspect of labeling pertaining to pediatric use when that labeling is protected by patent or exclusivity. A labeling statement stating that the ANDA is not labeled for pediatric use because of marketing exclusivity is required. In addition, the statute directs FDA to include in the ANDA labeling a statement of any appropriate pediatric contraindications, warnings, or precautions considered necessary." (This paragraph was reproduced verbatim from the consult.)

Ambien, the reference listed drug, was granted three years of Waxman-Hatch exclusivity on the basis of a clinical study performed to obtain pediatric safety, dosing and administration information in response to a Pediatric Written Request. The study performed was a placebo-controlled study in children (aged 6-17 years) with attention-deficit/hyperactivity disorder (ADHD) related insomnia. The information obtained was efficacy data, safety data and dosing and administration data. This information was added to the approved label.

Response to consult questions:
This information is presented in tabular format for ease of comparison with the innovator label. (Our recommended labeling is in regular font, with the rationale in *italics*.)

- The first column represents the section of the label in which the change is found.
- The second column represents the information from the Ambien label (Supplement-022, approved 3/2007)
- The third column represents the OGD recommendations based on BCPA
- The fourth column represents the recommendations from HFD-120, with the suggested labeling in regular font and our rationale in *italic* font.

PROFESSIONAL PACKAGE INSERT LABELING FOR AMBIEN Tablets (RLD: NDA 19-008,)

Section	AMBIEN LABELING (APP. 3/28/07)	OGD RECOMMENDATION BASED ON BPCA	HFD-120 RECOMMENDATION Labeling-regular font Rationale-italic font
HIGHLIGHT SECTION (PLR FORMAT)			
WARNINGS AND PRECAUTIONS	Pediatric patients with attention-deficit/hyperactivity disorder (ADHD): Hallucinations (7.4%) and other psychiatric and/or nervous system adverse events were observed frequently (5.6, 8.4)	Pediatric patients with attention-deficit/hyperactivity disorder (ADHD): Hallucinations (7.4%) and other psychiatric and/or nervous system adverse events were observed frequently (5.6, 8.4)	*The Division concurs with the proposed OGD labeling.*
HIGHLIGHTS-USE IN SPECIFIC POPULATIONS	Pediatric Use: Safety and effectiveness have not been established (8.4).	Pediatric Use: Safety and effectiveness have not been established (8.4).	*The Division concurs with the proposed OGD labeling.*
FULL PRESCRIBING INFORMATION			
WARNINGS AND PRECAUTIONS	5.3 Abnormal Thinking and Behavioral Changes: In controlled trials, <1% of adults with insomnia who received zolpidem reported hallucinations. In a clinical trial, 7.4% of pediatric patients with insomnia associated with attention-deficit/hyperactivity disorder (ADHD) who received zolpidem reported hallucinations.	5.3 Abnormal Thinking and Behavioral Changes: In controlled trials, <1% of adults with insomnia who received zolpidem reported hallucinations. In a clinical trial, 7.4% of pediatric patients with insomnia associated with attention-deficit/hyperactivity disorder (ADHD) who received zolpidem reported hallucinations.	*The Division concurs with the proposed OGD labeling.*

Section	AMBIEN LABELING (APP. 3/28/07)	OGD RECOMMENDATION BASED ON BPCA	HFD-120 RECOMMENDATION **Labeling-regular font with highlights** **Rationale-italic font**
WARNINGS AND PRECAUTIONS Special Populations, Pediatric Patients:	Special Populations, Pediatric patients: Safety and effectiveness of zolpidem has not been established in pediatric patients. In an 8-week study in pediatric patients (aged 6-17 years) with insomnia associated with ADHD, zolpidem did not decrease sleep latency compared with placebo. Hallucinations were reported in 7.4% of the pediatric patients who received zolpidem; none of the pediatric patients who received placebo reported hallucinations.[see Use in Specific Populations…]	Special Populations, Pediatric patients: Safety and effectiveness of zolpidem has not been established in pediatric patients. Hallucinations were reported in 7.4% of the pediatric patients who received zolpidem; none of the pediatric patients who received placebo reported hallucinations.[see Use in Specific Populations…] [ ]	Special Populations, Pediatric patients: Safety and effectiveness of zolpidem has not been established in pediatric patients. —————— ——————, zolpidem did not decrease sleep latency compared with placebo. Hallucinations were reported in 7.4% of the pediatric patients who received zolpidem; none of the pediatric patients who received placebo reported hallucinations.[see Use in Specific Populations…] [ ] *The information regarding the lack of demonstrated efficacy is important for the practitioner's assessment of risk/benefit.*

Section	AMBIEN LABELING (APP. 3/28/07)	OGD RECOMMENDATION BASED ON BPCA	HFD-120 RECOMMENDATION Labeling-regular font with highlights Rationale-italic font
USE IN SPECIFIC POPULATIONS	Special Populations, Pediatric patients: Safety and effectiveness of zolpidem has not been established in pediatric patients. In an 8-week controlled study, 201 pediatric patients (aged 6-17 years) with insomnia associated with ADHD (90% of the patients were using psychoanaleptics), were treated with an oral solution of zolpidem, 0.25 mg/kg/day, up to a maximum of 10 mg/day (n=136) or placebo (n=65). Zolpidem did not significantly decrease latency to persistent sleep, compared to placebo, as measured by polysomnography after 4 weeks of treatment. Psychiatric and nervous system disorders comprised the most frequent (>5%) treatment emergent adverse events observed with zolpidem versus placebo and included dizziness (23.5% vs. 1.5%), headache (12.5% vs. 9.2%), and hallucinations (7.4% vs. 0)[see Warnings and precautions: Special Populations (5.6)]. Ten patients on zolpidem (7.4%) discontinued treatment due to an adverse event.	Special Populations, Pediatric patients: Safety and effectiveness of zolpidem has not been established in pediatric patients. In an 8-week controlled study, 201 pediatric patients (aged 6-17 years) with insomnia associated with ADHD (90% of the patients were using psychoanaleptics), were treated with an oral solution of zolpidem, 0.25 mg/kg/day, up to a maximum of 10 mg/day (n=136) or placebo (n=65). Psychiatric and nervous system disorders comprised the most frequent (>5%) treatment emergent adverse events observed with zolpidem versus placebo and included dizziness (23.5% vs. 1.5%), headache (12.5% vs. 9.2%), and hallucinations (7.4% vs. 0)[see Warnings and precautions: Special Populations (5.6)]. Ten patients on zolpidem (7.4%) discontinued treatment due to an adverse event. [redacted]	Special Populations, Pediatric patients: Safety and effectiveness of zolpidem has not been established in pediatric patients. [redacted] Psychiatric and nervous system disorders comprised the most frequent (>5%) treatment emergent adverse events observed with zolpidem versus placebo and included dizziness (23.5% vs. 1.5%), headache (12.5% vs. 9.2%), and hallucinations (7.4% vs. 0)[see Warnings and precautions: Special Populations (5.6)]. Ten patients on zolpidem (7.4%) discontinued treatment due to an adverse event. [redacted]

Section	AMBIEN LABELING (APP. 3/28/07)	OGD RECOMMENDATION BASED ON BPCA	HFD-120 RECOMMENDATION Labeling-regular font with highlights Rationale-italic font
	PATIENT COUNSELING INFORMATION		
Children	Children: Ambien has not been shown to help children fall asleep. Hallucinations, headache and dizziness have all been reported as side effects in children who were given Ambien.	Children: Zolpidem tartrate tablets have not been shown to help children fall asleep. Hallucinations, headache and dizziness have all been reported as side effects in children who were given zolpidem tartrate tablets.	*The Division concurs with the proposed OGD labeling.*

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/s/

Dawn McNeil
4/11/2007 01:20:00 PM
MEDICAL OFFICER

Russell Katz
4/12/2007 09:50:57 AM
MEDICAL OFFICER

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

/s/

Ruby Wu
4/23/2007 08:24:03 AM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

M E M O R A N D U M

Date: April 13, 2007

From: Hari Cheryl Sachs, MD, Medical Officer
Debbie Avant, R.Ph, Regulatory Project Manager
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff

Through: Lisa Mathis, MD, OND Associate Director
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff

To: Gary Buehler, RPh, Director
Office of Generic Drugs

Re: Proposed labeling for zolpidem tartrate 5 and 10 mg tablets

Office Question:
The Office of Generic Drugs (OGD) has consulted the Pediatric and Maternal Health Staff (PMHS) to request a review of the proposed labeling for the generic product zolpidem tartrate tablets

Material Reviewed:
Consult from OGD
Ambien® labeling (Dec 1999), pediatric labeling changes for Ambien® (March 2007)
Comparison chart of labeling for the generic drug and Ambien®
Patent and exclusivity data for NDA 19-908 Ambien® 5 and 10 mg tablets

Background:
Best Pharmaceuticals for Children Act
Signed into law on January 4, 2002, the Best Pharmaceuticals for Children Act (BPCA) addresses the approval of drugs under 505(j) when pediatric information protected by exclusivity has been added to the labeling. BPCA section 11(a)(2) [21 USC 355a(l)(2)] states:

"(2) LABELING...The Secretary may require that the labeling of a drug approved under section 505(j) that omits a pediatric indication or other aspect of labeling... include--

(A) a statement that, because of marketing exclusivity for a manufacturer, ...

(i) the drug is not labeled for pediatric use; or

(ii) in the case of a drug for which there is an additional pediatric use, ... the drug is not labeled for the pediatric use ...

(B) a statement of any appropriate pediatric contraindications, warnings, or precautions that the Secretary considers necessary."

Regulatory History for zolpidem tartrate

On December 16, 1992, the FDA approved Sanofi Aventis US' Ambien® (zolpidem tartrate tablets, NDA 19-908) for the short-term treatment of insomnia characterized by difficulties with sleep initiation. The labeling indicated that safety and effectiveness in pediatric patients have not been established.

On March 28, 2007, the FDA approved revisions to the Ambien® Tablets (NDA 19-908) labeling to reflect that zolpidem did not decrease sleep latency compared to placebo in an 8-week study of pediatric patients and to describe psychiatric and central nervous system adverse events, including hallucinations. Ambien® Tablets (NDA 19-908) marketed by Sanofi Aventis US, was awarded three years of Waxman-Hatch exclusivity, which expires on March 29, 2010, based upon the sponsor's pediatric clinical study performed in response to the zolpidem written request. In addition, the sponsor was awarded pediatric exclusivity for the zolpidem moiety, resulting in six additional months protection for every zolpidem product by Sanofi Aventis US with patent protection or exclusivity. The additional protection for this product expires April 21, 2007 and September 29, 2010 respectively.

Several ANDAs have been submitted for zolpidem tartrate 5 and 10 mg tablets using Ambien® Tablets (NDA 19-908) as the reference listed drug.

Patent and Exclusivity Data for Ambien® Tablets (NDA 19-908)

PATENT	**Patent Expiration Date**
4382938	October 21, 2006
4382938 Pediatric	April 21, 2007
EXCLUSIVITY	**Exclusivity Expiration Date**
M-54	March 29, 2010
PED	September 29, 2010

Discussion:

The Ambien® labeling has been revised to comply with the new PLR format. In addition, parts of the labeling have been updated to reflect new information derived from the pediatric study that was performed. These sections include:

Highlights of Prescribing Information:

Warnings and Precautions

Use in Specific Populations: Pediatric Use

Full Prescribing Information:

5 Warnings and Precautions

5.3 Abnormal Thinking and Behavioral Changes
5.6 Special Populations: Pediatric patients
8 Use in specific Populations (8.4 Pediatric Use)
17 Patient Counseling Information

Highlights of Prescribing Information:
Under Warnings and Precautions, Highlights contains information regarding frequent observation of hallucinations and other psychiatric and/or nervous system adverse events in pediatric patients with attention-deficit/hyperactivity disorder (ADHD) OGD recommends retaining this information. A disclaimer is unnecessary.

Reviewer Comment: PMHS agrees with OGD's recommendations.

Under Use in Specific populations: Pediatric Use, Highlights contains the statement that safety and effectiveness have not been established. OGD recommends retaining this information. A disclaimer is unnecessary.

Reviewer Comment: PMHS agrees with OGD's recommendations.

5 Warnings and Precautions
5.3 Abnormal Thinking and Behavioral Changes
The current labeling describes the incidence of hallucinations in pediatric patients (7.4%). OGC recommends with retaining this information. A disclaimer is unnecessary.

Reviewer Comment: PMHS agrees with OGD's recommendations. An increased incidence of hallucinations is important safety information that should be included.

5.6 Special Populations: Pediatric patients
In addition to indicating that safety and effectiveness has not been established, the labeling includes a description of the clinical trial, indicating the lack of efficacy on sleep latency as well as the increased incidence of hallucinations in the treatment group. OGD recommends retaining the information about the adverse event. However, OGD recommends removing the description of the clinical trial with the inclusion of a disclaimer.

Reviewer Comment: PMHS disagrees with OGD. Including both the information that the drug was ineffective as well as potentially unsafe is important information for the practitioner in order for the product to be used safely. Moreover, the disclaimer could be misinterpreted as indicating that the innovator is approved for use in children. All the information should be retained and, in that case, a disclaimer would be unnecessary.

8 Use in specific Populations (8.4 Pediatric Use)
Section 8.4 Pediatric Use includes the statement that the safety and effectiveness of zolpidem have not been established. In addition, a description of the clinical trial and the adverse events (psychiatric and nervous system) is also included. OGD recommends excluding the results of the trial, namely that zolpidem did not significantly decrease sleep latency with the inclusion of an appropriate disclaimer.

Reviewer Comment: PMHS disagrees with OGD. As stated above, including both the information that the drug was ineffective as well as potentially unsafe is important information for the practitioner in order for the product to be used safely. A disclaimer would be unnecessary.

17 Patient Counseling Information

This section contains the statement that zolpidem tartrate tablets have not been shown to help children fall asleep, along with a description of common side effects. OGD recommends including this information. A disclaimer is unnecessary.
Reviewer Comment: PMHS concurs.

Recommendation
PMHS believes that all of the information related to pediatric studies should be retained in the generic labeling as all the information impacts on the weighing of risk/benefit and the safe use of this product.

FDA
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM

DATE: April 16, 2007

TO: Ruby (Chi-Ann) Wu, R.Ph., Office of Generic Drugs

THROUGH: Russell Katz, M.D., Division Director DNDP

FROM: D. Elizabeth McNeil, M.D., DNDP

RE: Proposed labeling for zolpidem tartrate products

Providing safety information without information regarding lack of efficacy would be inadequate to convey the risk/benefit profile of these medications for pediatric use. The prescribing information for all formulations of zolpidem tartrate tablets should contain all of the known efficacy/safety data for the pediatric population and therefore should reproduce most of the information in the current Ambien label (approved March 2007) to adequately inform practitioners about the apparent absence of demonstrated benefit in the face of an increased risk of central nervous system (CNS) adverse effects.

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/s/

Dawn McNeil
4/16/2007 06:10:36 PM
MEDICAL OFFICER

Russell Katz
4/17/2007 12:18:06 PM
MEDICAL OFFICER

OGD APPROVAL ROUTING SUMMARY

ANDA # 76-062 Applicant Par Pharmaceutical, Inc.
Drug Zolpidem Tartrate Tablets Strength(s) 5mg & 10mg

APPROVAL ☑ **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)** ☐ **OTHER** ☐

REVIEWER: **DRAFT Package** **FINAL Package**

1. Martin Shimer
Chief, Reg. Support Branch
Date 6 Sept 2006 / 18APR07 Date 4/23/07 for
Initials MMS / MMS Initials RW

Contains GDEA certification: Yes ☑ No ☐ Determ. of Involvement? Yes ☐ No ☒
(required if sub after 6/1/92) Pediatric Exclusivity System
RLD = NDA# 19-908
Patent/Exclusivity Certification: Yes ☑ No ☐ Date Checked 4/18/07 waiver granted
If Para. IV Certification- did applicant Nothing Submitted ☐
Notify patent holder/NDA holder Yes ☐ No ☐ Written request issued ☐
Was applicant sued w/in 45 days: Yes ☐ No ☐ Study Submitted ☐
Has case been settled: Yes ☐ No ☐ Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☑
Date of latest Labeling Review/Approval Summary ongoing
Any filing status changes requiring addition Labeling Review Yes ☐ No ☑
Type of Letter: P III → 938 exp. 10/21/2006
Comments: Eligible for Full AP on 4/21/07 provided Par provides acceptable Labeling Eligible for Full AP on 10/21/06 MMS 18APR07

2. Project Manager, LMatheny Team 4
Review Support Branch
Date 8/31/06 Date
Initials [illegible] Initials

Original Rec'd date 12/22/2000 EER Status Pending ☐ Acceptable ☑ OAI ☐
Date Acceptable for Filing 12/26/2000 Date of EER Status ~~FULL~~ 9/8/06
Patent Certification (type) III Date of Office Bio Review
Date Patent/Exclus.expires 10/21/06 Date of Labeling Approv. Sum 10/17/06
Citizens' Petition/Legal Case Yes ☐ No ☑ Labeling Acceptable Email Rec'd Yes ☐ No ☐
(If YES, attach email from PM to CP coord) Labeling Acceptable Email filed Yes ☐ No ☐
First Generic (Prior) Yes ☑ No ☐ Date of Sterility Assur. App.
Priority Approval Yes ☐ No ☐ Methods Val. Samples Pending Yes ☐ No ☐
(If yes, prepare Press Release) MV Commitment Rcd. from Firm Yes ☐ No ☐

Acceptable Bio reviews tabbed Yes ☐ No ☐ Modified-release dosage form: Yes ☐ No ☐
Suitability Petition/Pediatric Waiver Interim Dissol. Specs in AP Ltr: Yes ☐
Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐
Previously reviewed and tentatively approved ☐ Date
Previously reviewed and CGMP def. /NA Minor issued ☐ Date
Comments:

3. David Read **(PP IVs Only)** Pre-MMA Language included ☐
OGD Regulatory Counsel, Post-MMA Language Included ☐
Comments: N/A - Paragraph 3 certifications.
Date 4/23/07 for
Initials RW

4. Div. Dir./Deputy Dir.
Chemistry Div. I II OR III
Comments: cmc satisfactory.
Date 4/23/07
Initials [signature]

REVIEWER: **FINAL ACTION**

5. Frank Holcombe **First Generics Only** Date 4/23/07 for
Assoc. Dir. For Chemistry Initials
Comments: (First generic drug review)
N/A. Multiple ANDAs have been tentatively approved for this drug product.

6. Vacant RLD: Ambien Tablets 5mg and 10mg Date
Deputy Dir., DLPS Sanofi Aventis US, LLC NDA 19-908 (001, 002) Initials

7. Peter Rickman Date 4/23/07 for
Director, DLPS Initials
Para.IV Patent Cert: Yes ☐ No ☐; Pending Legal Action: Yes ☐ No ☐; Petition: Yes ☐ No ☐
Comments: This ANDA was tentatively approved on April 26, 2002. Final approval was blocked at that time by Sanofi's '938 patent and the subsequent award of 180-day generic drug exclusivity. Refer to the administrative review completed at that time. The firm submitted CMC amendments dated 3/1/06 and 8/16/06 in response to changes made to the DHF. FPR found acceptable for final approval 4/20/07 (in DFS). Based upon the BPCA consult all negative related to pediatrics was deemed to be "safety risk associated" and will be retained in the labeling for the generic product. CMC found acceptable for approval (Chemist review #1).

8. Robert L. West Date 4/23/2007
Deputy Director, OGD Initials
Para.IV Patent Cert: Yes ☐ No ☒; Pending Legal Action: Yes ☐ No ☒; Petition: Yes ☐ No ☐
Press Release Acceptable ☐
Comments: Acceptable EES dated 9/8/06 (verified 4/23/07). No OAI. Alerts noted. For made a paragraph III certification to the '938 patent that expired on 4/21/07 (with pediatric exclusivity added). For has also addressed Sanofi's M-54 exclusivity with a labeling "carve out" under BPCA. This is acceptable. There are no other unexpired patents or exclusivity listed in the current "Orange Book" for this drug product.
This ANDA is recommended for approval.

9. Gary Buehler Date 4/23/07 for
Director, OGD Initials
Comments:
First Generic Approval ☒ PD or Clinical for BE ☐ Special Scientific or Reg Issue ☐
Press Release Acceptable ☒

10. Project Manager, Team Leigh Ann, Jeanne Date 4/23/07
Review Support Branch Initials
N/A Date PETS checked for first generic drug (just prior to notification to Firm)
Applicant notification:
4:56 pm Time notified of approval by phone 5:01 pm Time approval letter faxed
FDA Notification:
4/23/07 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
4/23/07 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.
N/A Date Press Release emailed to CDER Liaison (M.Gonitzke)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

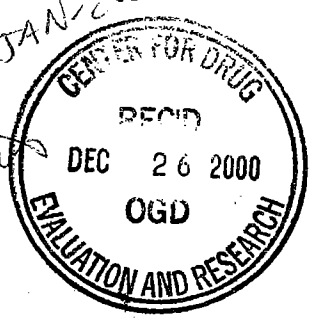
ANDA 76-062

CORRESPONDENCE

Par
Pharmaceutical,
Inc.

One Ram Ridge Road, Spring Valley, NY 10977
(914) 425-7100 • Telecopier (914) 425-7907

505(b)(2)(A) OK
22-JAN-2001



December 22, 2000

Copy 1
Copy 2
Copy 3 (field)*

Food and Drug Administration
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2
7500 Standish Place, Room 150
Rockville, Maryland 20855

RE: ZOLPIDEM TARTRATE TABLETS, 5 MG AND 10 MG
ELECTRONIC SUBMISSION OF BIOEQUIVALENCE STUDIES (ESD) WITHIN 30 DAYS

Dear Sir or Madam:

We herewith submit, in duplicate, an abbreviated new drug application for Zolpidem Tartrate Tablets, 5 mg and 10 mg. The application is submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

The official name of the drug relied upon as the basis upon which this application may be filed is Zolpidem Tartrate. The proprietary name of said drug is Ambien®. A copy of the appropriate pages of the Approved Drug Products with Therapeutic Equivalence Evaluations List is enclosed in SECTION II to show that the proposed drug is the same as the listed drug.

The certification concerning the patent is set forth under SECTION III. The approved insert labeling for the listed drug is enclosed in SECTION V. The third (field) copy certification is provided in SECTION XXI.

A randomized, 2-way crossover, bioequivalence study was conducted with Par Pharmaceutical, Inc. (USA) and G.D. Searle & Co. (USA) (Ambien®) 10 mg zolpidem tartrate tablets administered as a 1 x 10 mg tablet in healthy adult males under fasting conditions. A randomized, 3-way crossover, bioequivalence study was also conducted of Par Pharmaceutical, Inc. (USA) and G.D. Searle & Co. (USA) (Ambien®) 10 mg zolpidem tartrate tablets administered as a 1 x 10 mg tablet in healthy adult males under fasting and fed conditions. These studies are also applicable to the 5 mg strength as the formulations are proportionally similar. A request for the waiver of the bioequivalency requirements for the 5 mg strength is submitted along with comparative ***in-vitro*** dissolution data and financial disclosure statements in SECTION VI.

Finally, enclosed please find three (3) separately bound copies of the analytical methods and descriptive information required to test the bulk active and finished dosage form.

Please contact us if we may offer any assistance in your review of this application.

Very truly yours,
PAR PHARMACEUTICAL, INC.

Michelle Bonomi-Huvala
Director, Regulatory Affairs/R&D
Enclosures

* Brenda Holman
District Director
Food and Drug Administration
New York District Office
158-15 Liberty Avenue
Jamaica, New York 11433

76062

Par
Pharmaceutical,
Inc.

One Ram Ridge Road, Spring Valley, NY 10977
(845) 425-7100 • Fax (845) 425-7907

January 12, 2001

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

NEW CORRESP
NC/Bio

RE: ELECTRONIC SUBMISSION OF BIOEQUIVALENCE STUDIES
ZOLPIDEM TARTRATE TABLETS, 5 mg and 10 mg

Dear Staff:

Reference is made to our Abbreviated New Drug Application dated December 22, 2000 for Zolpidem Tartrate Tablets, 5 mg and 10 mg. A photostatic copy of the original application cover letter and corresponding FDA Form 356h are attached for your reference.

As indicated in our cover letter to the application, Par Pharmaceutical, Inc. herewith submits the Electronic Submission Document (ESD) for bioequivalence information contained in SECTION VI of our December 22, 2000 paper submission. One diskette containing file 00225-00230.zip is provided.

Declarations from Par Pharmaceutical, Inc. and _____ (CRO) stating that the data contained in the electronic files are identical to the data contained in SECTION VI of the paper submission are also enclosed.

If you have any questions or require anything further, please do not hesitate to contact us.

Sincerely,
PAR PHARMACEUTICAL, INC.

Janis A. Picurro
Senior Associate, Regulatory Affairs R&D
/encls.

ANDA 76-062

Par Pharmaceutical, Inc.
Attention: Michelle Bonomi-Huvala
One Ram Ridge Road
Spring Valley, New York 10977

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Zolpidem Tartrate Tablets, 5 mg and 10 mg

DATE OF APPLICATION: December 22, 2000

DATE (RECEIVED) ACCEPTABLE FOR FILING: December 26, 2000

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above..

Should you have questions concerning this application, contact:

Elaine Hu
Project Manager
(301) 827-5848

Sincerely yours,

Gregory S. Davis for

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 76-062
cc: DUP/Jacket
Division File
Field Copy
HFD-610/R.West
HFD-610/P.Rickman
HFD-92
HFD-615/M.Bennett
HFD-600/
Endorsement:
HFD-615/GDavis,Chief, RSB Davis 22-JAN-2001 date
HFD-615/PPatel,CSO Parae Patel date 1/19/01
Word File V:\Firmsnz\Par\ltrs&rev\76062.ACK
F/T EEH 01/19/2001
ANDA Acknowledgment Letter!

APPEARS THIS WAY
ON ORIGINAL

Par
Pharmaceutical,
Inc.

One Ram Ridge Road, Spring Valley, NY 10977
(845) 425-7100 • Fax (845) 425-7907

NC

NEW CORRESP

Copy 1 (archival)
Copy 2 (review)

BIOAVAILABILITY AMENDMENT

March 7, 2001

Food and Drug Administration
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855

RE: ANDA 76-062
Zolpidem Tartrate Tablets, 5 mg and 10 mg

Dear Staff:

Reference is made to our Abbreviated New Drug Application dated December 22, 2000 for Zolpidem Tartrate Tablets, 5 mg and 10 mg.

Par Pharmaceutical, Inc. is amending ANDA 76-062 with Amendment J to the Final Report for project 00230, the bioavailability study conducted in support of the above referenced application under fasting and fed conditions.

Also enclosed is a photostatic copy of the cover letter from ——— the company who conducted the study, explaining the documentation provided herein.

If you have any questions regarding the above, please do not hesitate to contact us.

This concludes our amendment to ANDA 76-062 for Zolpidem Tartrate Tablets, 5 mg and 10 mg.

Sincerely,
PAR PHARMACEUTICAL, INC.

Janis A. Picurro
Senior Associate, Regulatory Affairs R&D
/encl.

CENTER FOR DRUG
EVALUATION AND RESEARCH
MAR 0 8 2001
OGD

3-14-01

Par
Pharmaceutical,
Inc.

One Ram Ridge Road, Spring Valley, NY 10977
(845) 425-7100 • Fax (845) 425-7907

March 20, 2001

NEW CORRESP
NC/B10

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

76-062—ANDA

RE: ELECTRONIC SUBMISSION OF BIOEQUIVALENCE AMENDMENT
ZOLPIDEM TARTRATE TABLETS, 5 mg and 10 mg

Dear Staff:

Reference is made to our Abbreviated New Drug Application dated December 22, 2000 for Zolpidem Tartrate Tablets, 5 mg and 10 mg. Reference is also made to our bioequivalence amendment dated March 7, 2001, pertaining thereto. A photostatic copy of the amendment cover letter is attached for your reference.

In accordance with the above, Par Pharmaceutical, Inc. herewith submits the Electronic Submission Document (ESD) for Amendment I to the Final Report for project 00230; the information contained in our March 7th paper submission. One diskette containing file "Amendment-00230.zip" is provided.

Declarations from Par Pharmaceutical, Inc. and ———— (CRO) stating that the data contained in the electronic files are identical to the data contained in our March 7th paper submission are also enclosed.

If you have any questions or require anything further, please do not hesitate to contact us.

Sincerely,
PAR PHARMACEUTICAL, INC.

Janis A. Picurro
Senior Associate, Regulatory Affairs R&D
/encls.

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
MAR 22 2001
OGD

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Inc.

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N|AM

ORIG AMENDMENT

August 1, 2001

Food and Drug Administration
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855

MINOR AMENDMENT

RE: Zolpidem Tartrate, 5 mg and 10 mg
ANDA 76-062

Dear Staff:

Reference is made to the Agency's minor amendment facsimile dated June 5, 2001 which outlines deficiencies relating to our abbreviated new drug application dated December 22, 2000 for Zolpidem Tartrate Tablets, 5 mg and 10 mg. A photostatic copy of the Agency's June 5th correspondence is appended in Attachment I.

Par Pharmaceutical, Inc. is addressing the Agency's deficiencies with this minor amendment to ANDA 76-062. The Agency's comments and our responses follow.

Comment 1

DMF No.———— is inadequate. The DMF holder has been notified. Please do not respond to this letter until you have obtained a letter from the DMF holder stating that they have responded to the DMF deficiencies.

Response

Par Pharmaceutical, Inc. has been notified by letter dated July 31, 2001 from ———— has responded to all DMF deficiencies. A photostatic copy of ———— correspondence is provided in Attachment II.

Comment 2

Please include the test method and specifications for ———— and validate the test method.

Redacted 3 page(s)

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information from

8/1/2001 PAR LETTER

Comment 14

Please tighten the limits for ———————— for the drug product based on actual stability data.

Response

[ ] are provided in Attachment VIII and Attachment IX, respectively.

In addition, Par Pharmaceutical, Inc. notes and acknowledges that the firms referenced in the application relative to the manufacturing and testing of the product must be in compliance with cGMPs at the time of approval and since both the drug substance and product are not USP articles, the analytical methods require validation by the FDA laboratories.

Please note that Par forwarded all materials requested by FDA to perform method validation studies to the Northeast Regional Laboratory via overnight mail on June 21, 2001.

Bioequivalency Comments

Par acknowledges that the Division of Bioequivalence has completed its review and has no further questions at this time. Dissolution testing has been incorporated into our stability and quality control programs as indicated in the Agency's June 5th minor amendment facsimile.

We note that the bioequivalency comments provided in the Agency's communication are preliminary and are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues; and, that these reviews may result in the need of additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

We certify that the field copy is a true copy of the technical information contained in the archival and review copies of this amendment and was submitted to the New York District Office.

This concludes the amendment to our abbreviated new drug application for Zolpidem Tartrate Tablets, 5 mg and 10 mg, ANDA 76-062. If you have any questions regarding the above, please do not hesitate to contact us.

Sincerely,
PAR PHARMACEUTICAL, INC.

Janis A. Picurro
Senior Associate, Regulatory Affairs R&D
/encl.
* Jerome G. Woyshner
Acting District Director
Food and Drug Administration
New York District Office
158-15 Liberty Avenue
Jamaica, New York 11433

Par
Pharmaceutical,
Inc.

One Ram Ridge Road, Spring Valley, NY 10977
(845) 425-7100 • Fax (845) 425-7907

Copy 1 (review)
Copy 2 (archival)

August 23, 2001

Food and Drug Administration
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855

LABELING AMENDMENT

RE: Zolpidem Tartrate, 5 mg and 10 mg
ANDA 76-062

Dear Staff:

Reference is made to the Agency's facsimile dated July 10, 2001 which outlines labeling deficiencies relating to our abbreviated new drug application dated December 22, 2000 for Zolpidem Tartrate Tablets, 5 mg and 10 mg. A photostatic copy of the Agency's July 10th correspondence is appended in Attachment I.

Par Pharmaceutical, Inc. is addressing the Agency's comments with this labeling amendment to ANDA 76-062. The Agency's comments and our responses follow.

Labeling Deficiencies

1. CONTAINER (Bottles of 100s and 1000s)

   a. Enhance the prominence of the controlled substance symbol by increasing its size and setting it apart from the established name. Refer to 21 CFR 1302 for guidance.

   b. To be in compliance with 21 CFR 1302.06, please ensure that a tamper evident seal is affixed to the closure of each container.

   c. Please ensure that the established name and strength of the drug appear as the most prominent information on the label, i.e., decrease the size of "Rx".

CENTER FOR DRUG EVALUATION AND RESEARCH
AUG 24 2001

Response

The container labels are revised in accordance with the Agency's recommendations. Par submits, in final print, twelve (12) container labels each for the 5 mg (100s and 1000s) and 10 mg (100s and 1000s) strengths. Please refer to Attachment II. It is worth noting that 21 CFR 1302 has no requirements for the specific size or placement of the controlled substance symbol on container labeling. The container labels provided represent standard print format for all Par labeling.

In response to comment b., Par has proposed to use a [redacted] seal for each strength and container size. This type of seal is a foam liner with a pressure sensitive adhesive that causes the seal to adhere to the bottle when the cap is torqued. Upon opening the bottle, the foam seal is affixed to the bottle and "Sealed for your protection" is visible on the top of the seal. Once the seal is removed from the bottle, it leaves a foam residue on the lip of the bottle preventing any tampering and re-sealing of the bottle. Par believes that the seal used in the proposed packaging configurations fully complies with the provisions of 21 CFR 1302.6.

2. INSERT

   a. TITLE - Enhance the prominence of the controlled substance symbol.

   b. PRECAUTIONS

      i. Drug interactions (Drugs that affect the drug metabolism via cytochrome P450) - Revise so that the "$0 \rightarrow \infty$" appears as a subscript to "AUC" in the first sentence of the first paragraph.

      ii. Carcinogenesis, Mutagenesis, Impairment of Fertility (Mutagenesis) - Correct the spelling of "rat."

3. INFORMATION FOR PATIENTS TAKING ZOLPIDEM TARTRATE TABLETS

   a. GENERAL COMMENT: We note that INFORMATION FOR PATIENTS TAKING ZOLPIDEM TARTRATE TABLETS only appears at the end of the package insert. We also note that there is no notification to the pharmacist regarding the existence or instruction on how this information is to be distributed. Since this information alerts patients to potential side effects of this drug product, discusses special concerns of those using zolpidem, and gives tips on how to use it safely, please explain how this information is to be distributed to the patient. Include explanations for the 100 as well as the 1000 tablet package sizes.

   b. SIDE EFFECTS - "Lightheadedness" should appear as the third bullet.

Response

The INFORMATION FOR PATIENTS section is included as part of the package insert for the product. This information is also supplied as a separate brochure for the patient. As per our conversation with Ms. Lillie Golson, Labeling Review Branch, Par will supply 4 patient brochures per 100 tablets packaged. The patient brochures for the 100's package size are supplied on a single piece of paper containing the appropriate perforations and attached directly to the bottle along with the package insert. Brochures for the 1000's package size are supplied on a pad which is shrink wrapped with the bottles. Please note that Par supplies product only to wholesalers and not to pharmacies directly. Final print INFORMATION FOR PATIENTS brochures are provided in Attachment III.

In addition, Par submits, in final print, twelve (12) package inserts which are also appended in Attachment III. The insert is revised in accordance with the Agency's recommendations. All differences are annotated and explained in the side by side comparison provided in Attachment IV.

Par acknowledges that it may be necessary to revise our labeling if color and other factors (print size, prominence, etc.) are found unacceptable and that further changes might be requested prior to approval.

In addition, Par acknowledges that it may be necessary to further revise our labeling prior to approval due to subsequent approved changes in the reference listed drug. We will monitor the appropriate website for any approved changes.

In accordance with 21 CFR §314.94 (a)(8)(iv), and to facilitate review, side by side comparisons of the container labels and package insert with our December 22, 2000 submission, with all differences annotated and explained, are provided in Attachment IV.

This concludes the labeling amendment to our abbreviated new drug application for Zolpidem Tartrate Tablets, 5 mg and 10 mg, ANDA 76-062. If you have any questions regarding the above, please do not hesitate to contact us.

Sincerely,
PAR PHARMACEUTICAL, INC.

Janis A. Picurro
Senior Associate, Regulatory Affairs R&D
/encl.

Par
Pharmaceutical,
Inc.

One Ram Ridge Road, Spring Valley, NY 10977
(845) 425-7100 • Fax (845) 425-7907

Copy 1 ✓
Copy 2
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November 30, 2001

ORIG AMENDMENT

N/AM

Food and Drug Administration
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855

MINOR AMENDMENT

RE: Zolpidem Tartrate, 5 mg and 10 mg
ANDA 76-062

Dear Staff:

Reference is made to the Agency's minor amendment facsimile dated October 15, 2001 which outlines deficiencies relating to our abbreviated new drug application dated December 22, 2000 for Zolpidem Tartrate Tablets, 5 mg and 10 mg. Reference is also made to our minor amendment dated August 1, 2001, pertaining thereto. A photostatic copy of the Agency's October 15th correspondence is appended in Attachment I.

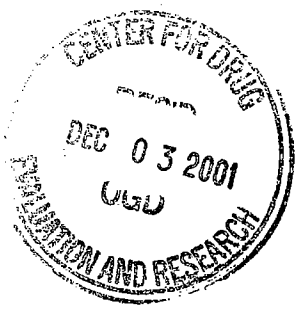
Par Pharmaceutical, Inc. is addressing the Agency's deficiencies with this minor amendment to ANDA 76-062. The Agency's comments and our responses follow.

Comment 1

DMF No. ——— remains inadequate. The DMF holder has been notified. Please do not respond to this letter until you have obtained a letter from the DMF holder stating that they have responded to the DMF deficiencies.

Response

——— has provided Par Pharmaceutical, Inc. with a letter dated November 2, 2001 documenting ——— response to FDA's October 15th deficiency letter. A photostatic copy of ——— correspondence is provided in Attachment II.



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11/30/2001 PAR LETTER

Par
Pharmaceutical,
Inc.

One Ram Ridge Road, Spring Valley, NY 10977
(845) 425-7100 • Fax (845) 425-7907

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Copy 3 (field)*

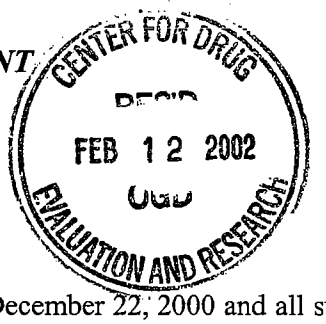
N/Am

ORIG AMENDMENT

February 11, 2002

Via Facsimile and Overnight Mail
Food and Drug Administration
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855

TELEPHONE AMENDMENT



RE: Zolpidem Tartrate, 5 mg and 10 mg
ANDA 76-062

Dear Staff:

Reference is made to our abbreviated new drug application dated December 22, 2000 and all subsequent amendments relative to Zolpidem Tartrate Tablets, 5 mg and 10 mg. Reference is also made to a telephone conversation with Ms. Sarah Ho (Project Manager) and Dr. Gil Kang (Chemistry Reviewer) regarding certain issues associated with our minor amendment dated November 30, 2001.

In accordance with the above, Par Pharmaceutical, Inc. is addressing the Agency's comments with this telephone amendment to ANDA 76-062. The Agency's comments and our responses follow.

Comment 1

Please revise the Raw Material Specifications/Procedures for Zolpidem Tartrate to include a limit ——— ——————————— and provide the corresponding test method.

Response

The Raw Material Specifications/Procedures for Zolpidem Tartrate (Document # RM-1238-007) is revised to include a test method and limit for ——————— in the acceptance criteria. The revised monograph is enclosed in Attachment I.

Comment 2

Please include a [redacted] test for the [redacted].

Response

The [redacted] Specification for the [redacted] is revised to include a test and specification for [redacted]. Please refer to Attachment II for the updated monograph and corresponding test data.

Comment 3

Please provide updated room temperature stability data.

Response

Updated room temperature stability data for the 5 mg and 10 mg tablets are provided in Attachment III.

We certify that the field copy is a true copy of the technical information contained in the archival and review copies of this amendment and was submitted to the New York District Office.

This concludes the telephone amendment to our abbreviated new drug application for Zolpidem Tartrate Tablets, 5 mg and 10 mg, ANDA 76-062. If you have any questions regarding the above, please do not hesitate to contact us.

Sincerely,
PAR PHARMACEUTICAL, INC.

Janis A. Picurro
Senior Associate, Regulatory Affairs R&D
/encl.

* Edward W. Thomas
Acting District Director
Food and Drug Administration
New York District Office
158-15 Liberty Avenue
Jamaica, New York 11433

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Inc.

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Copy 1 ✓
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Copy 3 (field)*

ORIG AMENDMENT
N/Am

March 11, 2002

Via Facsimile and Overnight Mail
Food and Drug Administration
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855

TELEPHONE AMENDMENT

RE: Zolpidem Tartrate, 5 mg and 10 mg
ANDA 76-062

Dear Staff:

Reference is made to our abbreviated new drug application dated December 22, 2000 and all subsequent amendments relative to Zolpidem Tartrate Tablets, 5 mg and 10 mg. Reference is also made to a telephone conversation with Mr. Paul Schwartz, Dr. James Fan and Dr. Gil Kang regarding remaining issues to be addressed prior to approval of the referenced application.

In accordance with the above, Par Pharmaceutical, Inc. is addressing the Agency's comments with this telephone amendment to ANDA 76-062. The Agency's comments and our responses follow.

Comment 1

Please revise the ———— for the finished product to ————. The ———— is acceptable for stability.

Response

The Finished Product/Stability Specifications/Procedures for Zolpidem Tartrate Tablets, 5 mg (Document # F/S-680-006) and 10 mg (Document # F/S-681-007) is revised to include the revised ———— ————. Please refer to Attachment I.

RECEIVED
MAR 12 2002
OGD / CDER

Comment 2

Please provide test results on the ——————————————— Results on the ——— lot used to manufacture the exhibit batch is preferable; however, results from a more recent lot is acceptable if the exhibit lot is not available.

Response

Test results for the ———————————————, manufacturer lot # 1026006001 used to manufacturer the ANDA exhibit batches, are presented under Section B, page 2, of the Method Validation Report (Report # M00-036.2). Please refer to Attachment II.

Comment 3

Please provide the Method Validation Report for the ——————— in the ———————
———

Response

The Method Validation Report (Report # M00-036.2) for the ——— test is provided in Attachment II.

We certify that the field copy is a true copy of the technical information contained in the archival and review copies of this amendment and was submitted to the New York District Office.

This concludes the telephone amendment to our abbreviated new drug application for Zolpidem Tartrate Tablets, 5 mg and 10 mg, ANDA 76-062. If you have any questions regarding the above, please do not hesitate to contact us.

Sincerely,
PAR PHARMACEUTICAL, INC.

Janis A. Picurro
Senior Associate, Regulatory Affairs R&D
/encl.

* Edward W. Thomas
Acting District Director
Food and Drug Administration
New York District Office
158-15 Liberty Avenue
Jamaica, New York 11433

PAR PHARMACEUTICAL

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www.parpharm.com

ORIG AMENDMENT
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March 17, 2006

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North 2
7500 Standish Place, Room 150
Rockville, Maryland 20855

RE: ANDA #76-062, Zolpidem Tartrate Tablets, 5 mg and 10 mg

Dear: Sir/Madam:

Reference is made to our abbreviated new drug application dated December 22, 2000 and all subsequent amendments relative to Zolpidem Tartrate Tablets, 5 mg and 10 mg. Reference is also made to the Agency's Tentative Approval letter dated April 26, 2002 pertaining thereto. A copy is provided for reference in Attachment 1.

Par is amending this application to incorporate updates to the In-house Standard, Raw Material, Finished Product/Stability monographs to be in line with the API manufacturer's revised DMF for zolpidem tartrate.

Par has been notified by the API manufacturer, ——— that a DMF revision was filed with the Agency. A current DMF authorization letter from ——— is enclosed in Attachment 2. Data previously submitted in the ANDA for Zolpidem Tartrate are well within the revised specifications.

In addition, we provide the following information in support of this amendment:

1. ———

2. ———

RECEIVED
MAR 20 2006
OGD / CDER

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information from

3/17/2006 PAR LETTER

We certify that the field copy of this amendment was submitted to the FDA New York District Office.

If you have any questions, please don't hesitate to contact me by phone at (845) 639-5128, fax (845) 639-5201 or by e-mail at jszozda@parpharm.com.

Sincerely,
PAR PHARMACEUTICAL

Julie Szozda
Senior Associate, Regulatory Affairs

Enc.

*Jerome G. Woyshner
District Director
Food and Drug Administration
New York District Office
158-15 Liberty Avenue
Jamaica, New York 11432

PAR PHARMACEUTICAL

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ORIG AMENDMENT
1N/1AF

August 28, 2006

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North 2
7500 Standish Place, Room 150
Rockville, Maryland 20855

Minor Amendment - Final Approval Requested

RE: ANDA #76-062, Zolpidem Tartrate Tablets, 5 mg and 10 mg

Dear: Sir/Madam:

Reference is made to our abbreviated new drug application dated December 22, 2000 and all subsequent amendments relative to Zolpidem Tartrate Tablets, 5 mg and 10 mg. Reference is also made to the Agency's Tentative Approval letter dated April 26, 2002 pertaining thereto. A copy is provided for reference.

In accordance with the Agency's request, we herewith submit this minor amendment via facsimile and hard copy to reactivate our application, ANDA 76-062, and request final approval upon expiration of U.S. Patent No. 4,382,938 on October 21, 2006.

Other than a change to Par's logo and format, there are no labeling changes to report and final printed labeling is provided in electronic format on the enclosed CD ROM. In addition, subsequent to our amendments dated March 17, 2006 and August 11, 2006, there have been no changes to this application.

Par also acknowledges that Zolpidem Tartrate Tablets, 5 mg and 10 mg may not be marketed without final Agency approval. Introduction or delivery into interstate commerce of the drug product will not occur before the effective date of approval of this application.

We certify that the field copy of this minor amendment-final approval requested was submitted to the FDA New York District Office.

This concludes our minor amendment to our abbreviated new drug application for Zolpidem Tartrate Tablets. If you have any questions, please don't hesitate to contact me at (845) 639-5128 or by e-mail at *jszozda@parpharm.com.*

Sincerely,
PAR PHARMACEUTICAL, INC.

Julie Szozda
Julie Szozda
Senior Associate, Regulatory Affairs

Enc.

*Jerome G. Woyshner
District Director
Food and Drug Administration
New York District Office
158-15 Liberty Avenue
Jamaica, New York 11432

PAR PHARMACEUTICAL

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Copy 1
Copy 2

September 13, 2006

ORIG AMENDMENT

N- 076 - AE

Ms. Ruby Wu
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North 2
7500 Standish Place, Room 150
Rockville, Maryland 20855

Labeling Amendment

RE: ANDA #76-062, Zolpidem Tartrate Tablets, 5 mg and 10 mg

Dear: Ms. Wu:

Reference is made to our August 28, 2006 minor amendment – final approval requested relative to Zolpidem Tartrate Tablets, 5 mg and 10 mg. Reference is also made to the Agency's facsimile of September 6, 2006 requesting that our container label for the 5 mg strength of Zolpidem Tartrate Tablets be revised to be in accord with the RLD. A copy of the September 6, 2006 facsimile is provided for reference.

In accordance with the Agency's request, we herewith submit this labeling amendment to ANDA 76-062.

The revised final printed container labels are provided in electronic format on the enclosed CD ROM. In addition, the final printed insert labeling submitted in the August 28, 2006 amendment, which is satisfactory, is provided in SPL format along with the required image file on the enclosed CD ROM as requested by Ruby Wu of the FDA in a conversation on September 11, 2006 and to be in line with the SPL labeling posted for the RLD.

This concludes our labeling amendment to our August 28, 2006 Minor Amendment – Final Approval Requested.for Zolpidem Tartrate Tablets. If you have any questions, please don't hesitate to contact me at (845) 639-5128 or by e-mail at *jszozda@parpharm.com.*

Sincerely,
PAR PHARMACEUTICAL, INC.

Julie Szozda
Senior Associate, Regulatory Affairs

Enc.

RECEIVED
SEP 14 2006
OGD / CDER

PAR PHARMACEUTICAL

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Copy 1
Copy 2

October 3, 2006

ORIG AMENDMENT
N.AF

Ruby Wu
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North 2
7500 Standish Place, Room 150
Rockville, Maryland 20855

Labeling Amendment – Replacement of SPL Labeling

RE: ANDA #76-062, Zolpidem Tartrate Tablets, 5 mg and 10 mg

Dear: Ms Wu:

Reference is made to our abbreviated new drug application dated December 22, 2000 and all subsequent amendments relative to Zolpidem Tartrate Tablets, 5 mg and 10 mg. Reference is also made to your telephone call regarding technical difficulties in the downloading of our SPL labeling file submitted electronically in the labeling amendment dated September 13, 2006.

In accordance with the Agency's request, the September 13, 2006 SPL labeling file previously submitted is being replaced with the current SPL file on the enclosed CD ROM.

Please note that there have been no changes to the labeling or to this application.

This concludes our labeling amendment to our abbreviated new drug application for Zolpidem Tartrate Tablets. If you have any questions, please don't hesitate to contact me at (845) 639-5128 or by e-mail at *jszozda@parpharm.com.*

Sincerely,
PAR PHARMACEUTICAL, INC.

Julie Szozda
Senior Associate, Regulatory Affairs

Enc.

RECEIVED
OCT 0 6 2006
OGD / CDER

PAR PHARMACEUTICAL

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tel 845 425 7100
fax 845 425 7907
www.parpharm.com

Copy 1
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MC

NAS 6/11/07

January 10, 2007

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North 2
7500 Standish Place, Room 150
Rockville, Maryland 20855

Labeling Amendment – Replacement of SPL Labeling

RE: ANDA #76-062, Zolpidem Tartrate Tablets, 5 mg and 10 mg

Dear Staff:

Reference is made to our abbreviated new drug application dated December 22, 2000 and all subsequent amendments relative to Zolpidem Tartrate Tablets, 5 mg and 10 mg. Reference is also made to a telephone call from the SPL Team regarding Tier 1 validation issues in ELIPS of our SPL labeling.

In accordance with the Agency's request, the SPL labeling file previously submitted on September 13, 2006 and October 3, 2006 is being replaced with the current SPL file on the enclosed CD ROM.

Please note that there have been no changes to the labeling or to this application.

This concludes our labeling amendment to our abbreviated new drug application for Zolpidem Tartrate Tablets. If you have any questions, please don't hesitate to contact me at (845) 639-5128 or by e-mail at *jszozda@parpharm.com.*

Sincerely,
PAR PHARMACEUTICAL, INC.

Julie Szozda

Julie Szozda
Senior Associate, Regulatory Affairs

Enc.

PAR PHARMACEUTICAL

Par Pharmaceutical, Inc.
One Ram Ridge Road
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Copy 1
Copy 2

April 18, 2007

Ruby (Chi-Ann) Wu
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North 2
7500 Standish Place, Room 150
Rockville, Maryland 20855

ORIG AMENDMENT
N-AF

Labeling Amendment

RE: ANDA #76-062, Zolpidem Tartrate Tablets, 5 mg and 10 mg

Dear Ms Wu:

Reference is made to the Agency's e-mail of April 16, 2007 requesting that our package insert labeling be revised for Zolpidem Tartrate Tablets, 5 mg and 10 mg.

In accordance with the Agency's request, we herewith submit this labeling amendment via facsimile and hard copy to ANDA 76-062.

Par's package insert has been updated according to the Agency's recommendations. Final printed labeling is provided electronically in PLR and in pdf format on the enclosed CD ROM. Par commits to submit SPL labeling post approval as a "Miscellaneous Correspondence" within 21 days after our ANDA has been approved.

This concludes our labeling amendment to our abbreviated new drug application for Zolpidem Tartrate Tablets. If you have any questions, please don't hesitate to contact me at (845) 639-5128 or by e-mail at *jszozda@parpharm.com.*

Sincerely,
PAR PHARMACEUTICAL, INC.

Julie Szozda
Submissions Manager, Regulatory Affairs

Enc.

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