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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

PURDUE PHARMACEUTICAL PRODUCTS L.P., PURDUE PHARMA L.P., and TRANSCEPT PHARMACEUTICALS, INC., Plaintiffs, v. PAR PHARMACEUTICAL, INC., Defendant.	Civil Action No. _____ Document Filed Electronically

COMPLAINT FOR PATENT INFRINGEMENT

Plaintiffs Purdue Pharmaceutical Products L.P.; Purdue Pharma L.P.; and Transcept Pharmaceuticals, Inc. (collectively, "Plaintiffs"), by their attorneys, for their complaint against Par Pharmaceutical, Inc. ("Par") allege as follows:

The Parties

1. Plaintiff Purdue Pharmaceutical Products L.P. is a limited partnership organized and existing under the laws of Delaware with its principal place of business at One Stamford Forum, 201 Tresser Boulevard, Stamford, CT 06901.

2. Plaintiff Purdue Pharma L.P. is a limited partnership organized and existing under the laws of Delaware with its principal place of business at One Stamford Forum, 201 Tresser Boulevard, Stamford, CT 06901.

3. Plaintiff Transcept Pharmaceuticals, Inc. is a corporation organized and existing under the laws of Delaware with its principal place of business at 1003 W. Cutting Blvd., Suite #110, Pt. Richmond, CA 94804.

4. Upon information and belief, Defendant Par Pharmaceutical, Inc. is a corporation organized and existing under the laws of Delaware with its principal place of business at 1 Ram Ridge Rd., Spring Valley, NY 10977.

5. Upon information and belief, Defendant Par is in the business of developing, manufacturing, and distributing generic pharmaceutical products throughout the United States, including in this judicial district. Upon information and belief, Par has a least one place of business in New Jersey, and is registered to do business in New Jersey under Business I.D. No. 0100071541. Upon information and belief, Par is also a registered manufacturer and wholesaler of drugs in New Jersey, with Registration Nos. 5001143 (manufacturer) and 5004032 (manufacturer and wholesaler). Upon information and belief, the CEO and Chairman of the Board of Defendant Par is located in Woodcliff Lake, New Jersey. Upon information and belief, Par shares a CEO and Board Chairman with parent company Par Pharmaceutical Companies, Inc., which has its principal place of business in Woodcliff Lake, New Jersey.

Jurisdiction and Venue

6. This is a civil action for patent infringement arising under the patent laws of the United States, Title 35 of the U.S. Code, for infringement of U.S. Patent No. 8,242,131 (the "'131 Patent") and U.S. Patent No. 8,252,809 (the "'809 Patent").

7. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a).

8. This Court has personal jurisdiction over Par by virtue of its widespread and continuous contacts with the state of New Jersey. Among other things, upon information and belief, Par has at least one business location in New Jersey and is registered to do business in New Jersey under Business I.D. No. 0100071541. Upon information and belief, Par is also a registered manufacturer and wholesaler of drugs in New Jersey, with Registration Nos. 5001143 (manufacturer) and 5004032 (manufacturer and wholesaler). Upon information and belief the CEO and Chairman of the Board of Par is located in Woodcliff Lake, New Jersey.

9. Par has previously submitted to, and purposefully availed itself of, the jurisdiction of the U.S. District Court for the District of New Jersey, including by filing counterclaims in this Court. *See, e.g.*, *Medeva Pharma Suisse A.G. et al. v. Par Pharm., Inc. et al.*, 3:10-cv-04008 (D.N.J.) (D.I. No. 11) (counterclaim filed by Par); *Abbott Labs. et al. v. Par Pharm. Inc.*, 2:04-cv-00325 (D.N.J.) (D.I. No. 4) (same); *Hoechst Marion v. Par Pharm. Inc.*, 2:95-cv-03673 (D.N.J.) (D.I. No. 16) (same).

10. Venue is proper in this judicial district pursuant to 28 U.S.C. §§ 1391 and 1400(b).

Regulatory Requirements for New and Generic Drugs

11. A person wishing to market a new drug that has not previously been approved by the U.S. Food and Drug Administration ("FDA") (a "pioneering" drug) must file a New Drug Application ("NDA") with FDA demonstrating that the drug is safe and effective for its intended use. 21 U.S.C. § 355(b).

12. A person wishing to market a generic copy of a drug that previously has been approved by FDA may follow a truncated approval process by filing an Abbreviated New Drug Application ("ANDA") for a generic version of that drug. In the ANDA, the applicant must demonstrate, among other things, bioequivalence of the generic copy with the pioneering drug. 21 U.S.C. § 355(j)(2)(A)(iv).

13. Unlike an NDA applicant, an ANDA applicant is not required to include safety and effectiveness data. Instead, the ANDA applicant is permitted to rely on the approval of the NDA applicant's drug—in essence, piggybacking on the NDA application and safety and effectiveness conclusions. 21 U.S.C. § 355(j).

14. Nor does an ANDA applicant establish any new conditions of use for the proposed drug product. Instead, an ANDA applicant may seek approval only for conditions of use that previously have been approved in connection with an approved NDA. 21 U.S.C. § 355(j)(2)(A)(i).

The Approved Drug Product

15. Purdue Pharmaceutical Products L.P. is the current holder of NDA No. 022328, for sublingual tablets containing 1.75 mg and 3.5 mg of zolpidem tartrate, which was first approved by FDA on November 23, 2011. Purdue Pharma L.P. markets the approved drug product under the tradename INTERMEZZO®. INTERMEZZO® is approved for treatment of insomnia when middle-of-the-night awakening is followed by difficulty returning to sleep. A copy of the prescribing information for INTERMEZZO® approved in NDA No. 022328 is attached as Exhibit A.

16. FDA has listed U.S. Patent Nos. 8,242,131 and 8,252,809 in the Orange Book—formally known as *Approved Drug Products With Therapeutic Equivalence Evaluations*—in connection with NDA No. 022328.

17. Transcept Pharmaceuticals, Inc. is the owner of the '131 and '809 Patents. Purdue Pharma L.P. and Purdue Pharmaceutical Products L.P. are exclusive licensees under the '131 and '809 Patents, the former to sell or offer to sell, and the latter to manufacture, zolpidem tartrate sublingual tablets.

ANDA No. 204229

18. Upon information and belief, on or before September 10, 2012, Par submitted to FDA an ANDA (ANDA No. 204229) with paragraph IV certifications under section 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. § 355(j)(2)(A)(vii)(IV), for 1.75 mg and 3.5 mg zolpidem tartrate sublingual tablets purportedly bioequivalent to INTERMEZZO®. The purpose of the ANDA is to obtain approval under section 505(j) of the FDCA to engage in the commercial manufacture and sale of a generic INTERMEZZO® product.

19. Upon information and belief, the indication set forth in the proposed labeling submitted in ANDA No. 204229 for Par's generic INTERMEZZO® product is the treatment of insomnia when middle-of-the-night awakening is followed by difficulty returning to sleep, *i.e.*, the same indication as that set forth in the approved labeling for INTERMEZZO®.

20. Upon information and belief, Par sent Plaintiffs Purdue Pharmaceutical Products L.P. and Transcept Pharmaceuticals, Inc. a letter dated September 10, 2012 (the "Notice Letter"). The Notice Letter represented that Par had submitted to FDA ANDA No. 204229 with paragraph IV certifications for the '131 and '809 Patents.

21. Upon information and belief, the purpose of the ANDA and paragraph IV certifications is to obtain approval under section 505(j) of the FDCA to engage in the commercial manufacture and sale of a generic version of INTERMEZZO® before the expiration of the patents listed in the Orange Book for NDA No. 022328. Hence, Par's purpose in submitting ANDA No. 204229 is to market the product described therein before expiration of the '131 and '809 Patents.

Count 1: Patent Infringement of the '131 Patent

22. Plaintiffs incorporate by reference all the allegations contained in paragraphs 1 to 21 above.

23. United States Patent No. 8,242,131, entitled "METHODS OF TREATING MIDDLE-OF-THE-NIGHT INSOMNIA," was duly and legally issued by the United States Patent and Trademark Office on August 14, 2012. Plaintiff Transcept Pharmaceuticals, Inc. is the owner of the '131 Patent. Plaintiffs Purdue Pharmaceutical Products L.P. and Purdue Pharma L.P. are exclusive licensees of the '131 Patent. A true and complete copy of the '131 Patent is attached hereto as Exhibit B.

24. Upon information and belief, Par submitted ANDA No. 204229 to FDA seeking approval to engage in the commercial manufacture, use, offer for sale, and sale of a generic version of INTERMEZZO® before the expiration of the '131 Patent.

25. Par's manufacture, use, offer for sale, or sale of such product would infringe the claims of the '131 Patent under 35 U.S.C. § 271(a), (b), and/or (c).

26. Upon information and belief, if approved, the generic INTERMEZZO® product for which approval is sought in Par's ANDA No. 204229 will be administered to human patients for the treatment of insomnia when middle-of-the-night awakening is followed by difficulty

returning to sleep, which administration would constitute direct infringement, either literally or under the doctrine of equivalents, of one or more claims of the '131 Patent. Upon information and belief, this infringement will occur at Par's behest, with its intent, knowledge, and encouragement, and Par will actively induce, encourage, aid and abet this administration with knowledge that it is in contravention of Plaintiffs' rights under the '131 Patent.

27. Par's manufacture, use, offer for sale, or sale in the United States, or importation into the United States, of the generic INTERMEZZO® product for which approval is sought in ANDA No. 204229 would actively induce and contribute to infringement of the '131 Patent, and Par would be liable as an infringer under 35 U.S.C. § 271(b) and/or (c).

28. Upon information and belief, as part of the ANDA filing, Par purportedly provided written certification to FDA that the claims of the '131 Patent are invalid and/or will not be infringed by the manufacture, use, or sale of Par's generic version of INTERMEZZO®.

29. Upon information and belief, by letter dated September 10, 2012, Par gave written notice of its certification of invalidity and/or non-infringement of the '131 Patent, alleging that all claims of the '131 Patent are invalid, and informing Plaintiffs that Par seeks approval to engage in the commercial manufacture, use, and sale of a product bioequivalent to INTERMEZZO® prior to the expiration of the '131 Patent.

30. Par has infringed the '131 Patent under 35 U.S.C. § 271(e)(2)(A) by virtue of submitting ANDA No. 204229 to market a generic version of INTERMEZZO® prior to the expiration of the '131 Patent. Moreover, if Par commercially uses, offers for sale, or sells its generic version of INTERMEZZO®, or induces or contributes to such conduct, it would further infringe the '131 Patent under 35 U.S.C. § 271(a), (b), and/or (c).

31. This case is an exceptional one, and Plaintiffs are entitled to an award of their reasonable attorneys' fees under 35 U.S.C. § 285.

32. Plaintiffs will be irreparably harmed if Defendant is not enjoined from infringing or actively inducing or contributing to infringement of the '131 Patent. Plaintiffs do not have an adequate remedy at law.

Count 2: Patent Infringement of the '809 Patent

33. Plaintiffs incorporate by reference all the allegations contained in paragraphs 1 to 32 above.

34. United States Patent No. 8,252,809, entitled "COMPOSITIONS FOR TREATING INSOMNIA," was duly and legally issued by the United States Patent and Trademark Office on August 28, 2012. Plaintiff Transcept Pharmaceuticals, Inc. is the owner of the '809 Patent. Plaintiffs Purdue Pharmaceutical Products L.P. and Purdue Pharma L.P. are exclusive licensees of the '809 Patent. A true and complete copy of the '809 Patent is attached hereto as Exhibit C.

35. Upon information and belief, Par submitted ANDA No. 204229 to FDA seeking approval to engage in the commercial manufacture, use, offer for sale, and sale of a generic version of INTERMEZZO® before the expiration of the '809 Patent.

36. Par's manufacture, use, offer for sale, or sale of such product would infringe the claims of the '809 Patent under 35 U.S.C. § 271(a), (b), and/or (c).

37. Upon information and belief, if approved, the generic INTERMEZZO® product for which approval is sought in Par's ANDA No. 204229 will be administered to human patients for the treatment of insomnia when middle-of-the-night awakening is followed by difficulty returning to sleep, which administration would constitute direct infringement, either literally or

under the doctrine of equivalents, of one or more claims of the '809 Patent. Upon information and belief, this infringement will occur at Par's behest, with its intent, knowledge, and encouragement, and Par will actively induce, encourage, aid and abet this administration with knowledge that it is in contravention of Plaintiffs' rights under the '809 Patent.

38. Par's manufacture, use, offer for sale, or sale in the United States, or importation into the United States, of the generic INTERMEZZO® product for which approval is sought in ANDA No. 204229 would actively induce and contribute to infringement of the '809 Patent, and Par would be liable as an infringer under 35 U.S.C. § 271(b) and/or (c).

39. Upon information and belief, as part of the ANDA filing, Par purportedly provided written certification to FDA that the claims of the '809 Patent are invalid and/or will not be infringed by the manufacture, use, or sale of Par's generic version of INTERMEZZO®.

40. Upon information and belief, by letter dated September 10, 2012, Par gave written notice of its certification of invalidity and/or non-infringement of the '809 Patent, alleging that all claims of the '809 Patent are invalid, and informing Plaintiffs that Par seeks approval to engage in the commercial manufacture, use, and sale of a product bioequivalent to INTERMEZZO® prior to the expiration of the '809 Patent.

41. Par has infringed the '809 Patent under 35 U.S.C. § 271(e)(2)(A) by virtue of submitting ANDA No. 204229 to market a generic version of INTERMEZZO® prior to the expiration of the '809 Patent. Moreover, if Par commercially uses, offers for sale, or sells its generic version of INTERMEZZO®, or induces or contributes to such conduct, it would further infringe the '809 Patent under 35 U.S.C. § 271(a), (b), and/or (c).

42. This case is an exceptional one, and Plaintiffs are entitled to an award of their reasonable attorneys' fees under 35 U.S.C. § 285.

43. Plaintiffs will be irreparably harmed if Par is not enjoined from infringing or actively inducing or contributing to infringement of the '809 Patent. Plaintiffs do not have an adequate remedy at law.

Prayer for Relief

WHEREFORE, Plaintiffs seek the following relief:

A. A judgment that Par has infringed the '131 and '809 Patents under 35 U.S.C. § 271(e)(2)(A);

B. An order pursuant to 35 U.S.C. § 271(e)(4)(A) providing that the effective date of any approval of ANDA No. 204229 is not earlier than the latest expiration date of the '131 and '809 Patents, or any later expiration of exclusivity for the '131 or '809 Patent to which Plaintiffs are or become entitled;

C. A permanent injunction restraining and enjoining Par and its officers, agents, servants, employees, parents, subsidiaries, divisions, affiliates, and those persons in active concert or participation with any of them, from making, using, selling, offering to sell, or importing any product that infringes the '131 or '809 Patent, including the product described in ANDA No. 204229;

D. A judgment declaring that the making, using, selling, offering to sell, or importing of the product described in ANDA No. 204229, or inducing or contributing to such conduct, would constitute infringement of the '131 and '809 Patents by Par pursuant to 35 U.S.C. § 271(a), (b), and/or (c);

E. A finding that this is an exceptional case, and an award of attorneys' fees in this action pursuant to 35 U.S.C. § 285;

F. Costs and expenses in this action; and

G. Such further and other relief as this Court determines to be just and proper.

Dated: October 25, 2012

Respectfully submitted,

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NOTICE OF OTHER ACTIONS PURSUANT TO L. CIV. R. 11.2

The undersigned hereby certifies that the matter in controversy is not the subject of any other action or proceeding in any court or of a pending arbitration proceeding, except that the same FDA-approved pharmaceutical drug product on which this Complaint is based is the subject of three other patent infringement actions involving a patent that is not at issue in this action, all of which are currently pending in this District and assigned to the same District Judge: *Purdue Pharmaceutical Products, Inc. et al. v. Actavis Elizabeth LLC*, 2:12-cv-5311-JLL-MAH; *Purdue Pharmaceutical Products, Inc. et al. v. Watson Pharmaceuticals, Inc. et al.*, 2:12-cv-5390-JLL-MAH; and *Purdue Pharmaceutical Products, Inc. et al. v. Novel Laboratories, Inc.*, 2:12-cv-5650-JLL-MAH. In addition, contemporaneously with the filing of this Complaint, Plaintiffs are also filing another Complaint based on the same United States Patents asserted in this case, *Purdue Pharmaceutical Products, Inc. et al. v. Par Formulations Private, Ltd.*, which has not yet been assigned a docket number or been assigned to a District Judge.

/s/ Michael Dore
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EXHIBIT A

INTERMEZZO - zolpidem tartrate tablet
Purdue Pharma LP

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use INTERMEZZO safely and effectively. See full prescribing information for INTERMEZZO.
INTERMEZZO® (zolpidem tartrate) sublingual tablets, CIV
Initial U.S. Approval: 1992

INDICATIONS AND USAGE

Intermezzo is a $GABA_A$ agonist indicated for use as needed for the treatment of insomnia when a middle-of-the-night awakening is followed by difficulty returning to sleep (1)
Limitation of Use: Not indicated for the treatment of middle-of-the night awakening when the patient has fewer than 4 hours of bedtime remaining before the planned time of waking (1)

DOSAGE AND ADMINISTRATION

- Take only if 4 hours of bedtime remain before the planned time of waking (2.1, 5.1)
- Intermezzo should be placed under the tongue and allowed to disintegrate completely before swallowing. The tablet should not be swallowed whole. (2.1)
- The effect of Intermezzo may be slowed if taken with or immediately after a meal (2.1)
- Recommended dose is 1.75 mg for women and 3.5 mg for men, taken only once per night if needed (2.2)
- Lower doses of CNS depressants may be necessary when taken concomitantly with Intermezzo (2.3)
- Co-administration with CNS depressants: Recommended dose is 1.75 mg for men and women (2.3)
- Geriatric patients and patients with hepatic impairment: Recommended dose is 1.75 mg for men and women (2.4, 2.5)

DOSAGE FORMS AND STRENGTHS

1.75 mg and 3.5 mg sublingual tablets (3)

CONTRAINDICATIONS

Known hypersensitivity to zolpidem (4)

WARNINGS AND PRECAUTIONS

- CNS depressant effects: Impairs alertness and motor coordination. Instruct patients on correct use (5.1)
- Evaluate for co-morbid diagnoses: Re-evaluate if insomnia persists after 7 to 10 days of use (5.2)
- Severe anaphylactic/anaphylactoid reactions: Angioedema and anaphylaxis have been reported. Do not re-challenge if such reactions occur (5.3)
- “Sleep-driving” and other complex behaviors while not fully awake. Risk increases with dose and use with other CNS depressants and alcohol. Immediately evaluate any new onset behavioral changes (5.4)
- Depression: Worsening of depression or suicidal thinking may occur. Prescribe the least number of tablets feasible to avoid intentional overdose (5.5)
- Respiratory Depression: Consider this risk before prescribing in patients with compromised respiratory function (5.6)

ADVERSE REACTIONS

Most commonly observed adverse reactions (> 1% in adult patients) are headache, nausea, and fatigue. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Purdue Pharma at 1-888-726-7535 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- CNS depressants, including alcohol: Possible adverse additive CNS depressant effects (5.1, 7.1)
- Imipramine: Decreased alertness observed (7.1)
- Chlorpromazine: Impaired alertness and psychomotor performance observed (7.1)
- Rifampin: Combination use may decrease effect (7.2)
- Ketoconazole: Combination use may increase effects (7.2)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, zolpidem may cause fetal harm. (8.1)

- Pediatric use: Safety and effectiveness of Intermezzo not established. With bedtime dosing of zolpidem, hallucinations observed (incidence 7%) (8.4)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 07/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION: CONTENTS*

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

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Intermezzo® (zolpidem tartrate) sublingual tablet is indicated for use as needed for the treatment of insomnia when a middle-of-the-night awakening is followed by difficulty returning to sleep.

Limitations of Use: Intermezzo is not indicated for the treatment of middle-of-the-night insomnia when the patient has fewer than 4 hours of bedtime remaining before the planned time of waking.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

Intermezzo is to be taken in bed when a patient wakes in the middle of the night and has difficulty returning to sleep. Intermezzo should only be taken if the patient has at least 4 hours of bedtime remaining before the planned time of waking *[see Warnings and Precautions (5.1)]*.

Intermezzo should be placed under the tongue and allowed to disintegrate completely before swallowing. The tablet should not be swallowed whole. For optimal effect, Intermezzo should not be administered with or immediately after a meal. The blister should be removed from the pouch just prior to dosing.

2.2 Basic Dosing Information

The recommended and maximum dose of Intermezzo is 1.75 mg for women and 3.5 mg for men, taken only once per night as needed if a middle-of-the-night awakening is followed by difficulty returning to sleep. The recommended doses for women and men are different

because women clear zolpidem from the body at a lower rate than men*[see Use in Specific Populations (8.6)]*.

2.3 Use with CNS Depressants

The recommended Intermezzo dose for men and women who are taking concomitant CNS depressants is 1.75 mg. Dose adjustment of concomitant CNS depressants may be necessary when co-administered with Intermezzo because of potentially additive effects. The use of Intermezzo with other sedative-hypnotics (including other zolpidem products) at bedtime or the middle of the night is not recommended *[see Warnings and Precautions (5.1)]*.

2.4 Use in Geriatric Patients

Geriatric patients may be especially sensitive to the effects of zolpidem. The recommended dose of Intermezzo in men and women over 65 years old is 1.75 mg, taken only once per night if needed *[see Use in Specific Populations (8.5)]*.

2.5 Use in Patients with Hepatic Impairment

The recommended dose of Intermezzo in patients with hepatic impairment is 1.75 mg, taken only once per night if needed *[see Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

Intermezzo is available as 1.75 mg and 3.5 mg tablets for sublingual administration.

Intermezzo 1.75 mg tablets are yellow, round, uncoated, biconvex, debossed with ZZ on one side.

Intermezzo 3.5 mg tablets are beige, round, uncoated, biconvex, debossed with ZZ on one side.

4 CONTRAINDICATIONS

Intermezzo is contraindicated in patients with known hypersensitivity to zolpidem. Observed reactions with zolpidem include anaphylaxis and angioedema *[see Warnings and Precautions (5.3)]*.

5 WARNINGS AND PRECAUTIONS

5.1 CNS Depressant Effects and Next-Day Impairment

Intermezzo, like other sedative-hypnotic drugs, has central nervous system (CNS) depressant effects. Co-administration with other CNS depressants (e.g., benzodiazepines, opioids, tricyclic antidepressants, alcohol) increases the risk of CNS depression. Dosage adjustments of Intermezzo and of other concomitant CNS depressants may be necessary when Intermezzo is administered with such agents because of the potentially additive effects. The use of Intermezzo with other sedative-hypnotics (including other zolpidem products) at bedtime or the middle of the night is not recommended *[see Dosage and Administration (2.3)]*.

In a driving study, healthy subjects who received Intermezzo with fewer than four hours of bedtime remaining had evidence of impaired driving compared to subjects who received placebo *[see Clinical Studies (14.2)]*. The risk of next-day driving impairment (and psychomotor impairment) is increased if Intermezzo is taken with less than 4 hours of bedtime

remaining; if higher than recommended dose is taken; if co-administered with other CNS depressants; or co-administered with other drugs that increase the blood levels of zolpidem.

5.2 Need to Evaluate for Co-morbid Diagnoses

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.

5.3 Severe Anaphylactic and Anaphylactoid Reactions

Cases of angioedema involving the tongue, glottis, or larynx have been reported in patients after taking the first or subsequent doses of zolpidem. 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 or anaphylaxis after treatment with zolpidem should not be rechallenged with Intermezzo.

5.4 Abnormal Thinking and Behavioral Changes

Abnormal thinking and behavior changes have been reported in patients treated with sedative-hypnotics including zolpidem. Some of these changes included decreased inhibition (e.g., aggressiveness and extroversion that seemed out of character), bizarre behavior, agitation, and depersonalization. Visual and auditory hallucinations have also been reported.

In controlled trials of zolpidem tartrate 10 mg taken at bedtime, < 1% of adults with insomnia who received zolpidem reported hallucinations. In a clinical trial, 7% of pediatric patients treated with zolpidem tartrate 0.25 mg/kg taken at bedtime, reported hallucinations, versus 0% treated with placebo *[see Use in Specific Populations (8.4)]*.

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 in sedative-hypnotic-naive as well as in sedative-hypnotic-experienced persons. Although behaviors such as “sleep-driving” have occurred with zolpidem alone at therapeutic doses, the co-administration of zolpidem with alcohol and other CNS depressants increases the risk of such behaviors, as does the use of zolpidem at doses exceeding the maximum recommended dose. Due to the risk to the patient and the community, discontinuation of Intermezzo 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 also occur.

The emergence of any new behavioral sign or symptom of concern requires careful and immediate evaluation.

5.5 Use in Patients with Depression

In primarily depressed patients treated with sedative-hypnotics, worsening of depression, and suicidal thoughts and actions (including completed suicides), have been reported. Suicidal tendencies may be present in such patients and protective measures may be required. Intentional overdosage is more common in this group of patients; therefore, the lowest number of tablets that is feasible should be prescribed for the patient at any one time.

5.6 Respiratory Depression

Although studies with 10 mg zolpidem tartrate did not reveal respiratory depressant effects at hypnotic doses in healthy subjects 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 compared to placebo. Since sedative-hypnotics have the capacity to depress respiratory drive, precautions should be taken if Intermezzo is prescribed to patients with compromised respiratory function. Post-marketing reports of respiratory insufficiency in patients receiving 10 mg of zolpidem tartrate, most of whom had pre-existing respiratory impairment, have been reported. The risks of respiratory depression should be considered prior to prescribing Intermezzo in patients with respiratory impairment including sleep apnea and myasthenia gravis.

5.7 Withdrawal Effects

There have been reports of withdrawal signs and symptoms following the rapid dose decrease or abrupt discontinuation of zolpidem. Monitor patients for tolerance, abuse, and dependence *[see Drug Abuse and Dependence (9.2) and (9.3)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions in zolpidem-treated patients are discussed in greater detail in other sections of the labeling:

- CNS-depressant effects and next-day impairment *[see Warnings and Precautions (5.1)]*
- Serious anaphylactic and anaphylactoid reactions *[see Warnings and Precautions (5.3)]*
- Abnormal thinking and behavioral changes, and complex behaviors *[see Warnings and Precautions (5.4)]*
- Withdrawal effects *[see Warnings and Precautions (5.7)]*

6.1 Clinical Trials Experience

The safety data described below are based on two double-blind placebo-controlled trials of Intermezzo in adult patients with insomnia characterized by difficulty returning to sleep after a middle-of-the-night awakening *[see Clinical Studies (14.1)]*. These two trials included 230 and 82 patients treated with 3.5 mg and 1.75 mg of Intermezzo, respectively. The first study was a 3-way crossover sleep-laboratory study in 82 patients (58 female and 24 male; median age 47 years; 51% Caucasian, 44% African-American) of 1.75 mg and 3.5 mg of Intermezzo compared to placebo (Study 1). The second study was a 4-week, parallel-group at-home study in 295 patients (201 female and 94 male; median age 43 years) of 3.5 mg of Intermezzo compared to placebo, used on an as-needed basis after spontaneous middle-of-the-night

awakenings (Study 2). In Study 2, patients took Intermezzo during the night on 62% of study nights.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in actual practice.

Table 1 shows the incidence of adverse reactions reported in Study 2 that occurred in 2% or more of Intermezzo-treated (3.5 mg) patients in which the incidence was greater than the incidence in placebo-treated patients. For women and other patients taking the 1.75 mg dose in Study 1, the incidence of adverse reactions was similar to the incidence seen with 3.5 mg of Intermezzo in Table 1.

The most commonly reported adverse reactions in all treatment groups were headache, nausea, and fatigue.

Table 1: Summary of Adverse Reactions (≥ 2%) in Outpatient, Double-Blind, Parallel-Group, Placebo-Controlled Study (Study 2)

MedDRA System Organ Class Preferred Term	3.5 mg Intermezzo (n=150)	Placebo (n=145)
Gastrointestinal Disorders	**4%**	**2%**
Nausea	1%	1%
General Disorders and Administration Site Conditions	**3%**	**0%**
Fatigue	1%	0%
Nervous System Disorders	**5%**	**3%**
Headache	3%	1%

7 DRUG INTERACTIONS

7.1 CNS-active Drugs

Co-administration of zolpidem with other CNS depressants increases the risk of CNS depression *[see Warnings and Precautions (5.1)]*. Zolpidem tartrate was evaluated in healthy volunteers in single-dose interaction studies for several CNS drugs.

Imipramine

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.

Haloperidol

A study involving haloperidol and zolpidem revealed no effect of haloperidol on the pharmacokinetics or pharmacodynamics of zolpidem. The lack of a drug interaction following

single-dose administration does not predict the absence of an effect following chronic administration.

Alcohol

An additive adverse effect on psychomotor performance between alcohol and oral zolpidem was demonstrated *[see Warnings and Precautions (5.1)]*.

Sertraline

Concomitant administration of zolpidem and sertraline increases exposure to zolpidem and may increase the pharmacodynamic effect of zolpidem.

Fluoxetine

After multiple doses of zolpidem tartrate and fluoxetine an increase in the zolpidem half-life (17%) was observed. There was no evidence of an additive effect in psychomotor performance *[see Clinical Pharmacology (12.3)]*.

7.2 Drugs that Affect Drug Metabolism via Cytochrome P450

Some compounds known to inhibit CYP3A may increase exposure to zolpidem. The effect of other P450 enzymes on the exposure to zolpidem is not known.

Rifampin

Rifampin, a CYP3A4 inducer, significantly reduced the exposure to and the pharmacodynamic effects of zolpidem. Use of Rifampin in combination with zolpidem may decrease the efficacy of zolpidem.

Ketoconazole

Ketoconazole, a potent CYP3A4 inhibitor, increased the pharmacodynamic effects of zolpidem. Consideration should be given to using a lower dose of zolpidem when ketoconazole and zolpidem are given together.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies of zolpidem in pregnant women. Studies in children to assess the effects of prenatal exposure to zolpidem have not been conducted; however, cases of severe neonatal respiratory depression have been reported when zolpidem was used at the end of pregnancy, especially when taken with other CNS-depressants. Children born to mothers taking sedative-hypnotic drugs may be at risk for withdrawal symptoms during the postnatal period. Neonatal flaccidity has also been reported in infants born to mothers who received sedative-hypnotic drugs during pregnancy. Intermezzo should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

Administration of zolpidem to pregnant rats and rabbits resulted in adverse effects on offspring at doses greater than the recommended human dose (RHD) of 3.5 mg/day (approximately 2.8 mg/day zolpidem base); however, teratogenicity was not observed.

When zolpidem was administered at oral doses of 4, 20, and 100 mg base/kg/day to pregnant rats during the period of organogenesis, dose-related decreases in fetal skull ossification were observed at all but the lowest dose, which is approximately 15 times the RHD on a mg/m^2 basis. In rabbits treated during organogenesis with zolpidem at oral doses of 1, 4, and 16 mg base/kg/day, increased embryo-fetal death and incomplete fetal skull ossification were seen at the highest dose tested. The no-effect dose for embryo-fetal toxicity in rabbits is approximately 30 times the RHD on a mg/m^2 basis. Administration of zolpidem to rats at oral doses of 4, 20, and 100 mg base/kg/day during the latter part of pregnancy and throughout lactation produced decreased offspring growth and survival at all but the lowest dose, which is approximately 15 times the RHD on a mg/m^2 basis.

8.3 Nursing Mothers

Zolpidem is excreted in human milk. The effect of zolpidem on the nursing infant is not known.

8.4 Pediatric Use

Intermezzo is not recommended for use in children. Safety and effectiveness of Intermezzo have not been established in pediatric patients below the age of 18.

In an 8-week study in pediatric patients (aged 6 to 17 years) with insomnia associated with ADHD, an oral solution of zolpidem tartrate dosed at 0.25 mg/kg at bedtime did not decrease sleep latency compared to placebo. Hallucinations were reported in 7% of the pediatric patients who received zolpidem; none of the pediatric patients who received placebo reported hallucinations.

8.5 Geriatric Use

Intermezzo dosage adjustment is necessary in geriatric patients. Sedating drugs may cause confusion and over-sedation in the elderly; elderly patients generally should be started on low doses of Intermezzo and observed closely *[see Dosage and Administration (2.4), and Clinical Pharmacology (12.3)]*.

Clinical trial experience with other zolpidem formulations (5 mg to 10 mg oral zolpidem tartrate) given at bedtime:

A total of 154 patients in U.S. controlled clinical trials and 897 patients in non-U.S. clinical trials who received oral zolpidem were ≥ 60 years of age. For a pool of U.S. patients receiving oral zolpidem tartrate at doses of ≤ 10 mg or placebo, there were three adverse reactions occurring at an incidence of at least 3% for zolpidem and for which the zolpidem incidence was at least twice the placebo incidence (see Table 2).

Table 2: Adverse Reactions in Geriatric Patients in Pooled Trials of 5 mg to 10 mg of Oral Zolpidem Tartrate Given at Bedtime

Adverse Reaction	5 to 10 mg Oral Zolpidem tartrate	Placebo
Dizziness	3%	0%

Drowsiness	5%	2%
Diarrhea	3%	1%

Falls in geriatric patients:

A total of 30/1,959 (2%) non-U.S. patients receiving other zolpidem formulations (5 mg to 10 mg oral zolpidem tartrate) reported falls, including 28/30 (93%) who were ≥ 70 years of age. Of these 28 patients, 23 (82%) were receiving zolpidem tartrate doses > 10 mg. A total of 24/1,959 (1%) 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 tartrate doses >10 mg.

The dose of Intermezzo in elderly patients is 1.75 mg to minimize adverse effects related to impaired motor and/or cognitive performance and unusual sensitivity to sedative-hypnotic drugs.

8.6 Gender Difference in Pharmacokinetics

Women cleared zolpidem tartrate from the body after sublingual administration of a 3.5 mg dose of Intermezzo at a lower rate than men (2.7 mL/min/kg vs. 4.0 mL/min/kg). C_{max} and AUC parameters of zolpidem were approximately 45% higher at the same dose in female subjects compared with male subjects. Given the higher blood levels of zolpidem tartrate in women compared to men at a given dose, the recommended dose of Intermezzo for women is 1.75 mg, and the recommended dose for adult men is 3.5 mg.

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. Tolerance is a state of adaptation in which exposure to a drug induces changes that result in 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 40 mg of oral zolpidem tartrate were similar, but not identical, to diazepam 20 mg, while 10 mg of oral zolpidem tartrate was difficult to distinguish from placebo.

Because persons with a history of addiction to or abuse of drugs or alcohol are at increased risk for misuse, abuse and addiction of zolpidem, they should be monitored carefully when receiving Intermezzo.

9.3 Dependence

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.

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 following adverse events which are considered to meet the DSM-III-R criteria for uncomplicated sedative-hypnotic withdrawal were reported during U.S. clinical trials with other oral zolpidem formulations following placebo substitution occurring within 48 hours following the 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. Post-marketing reports of abuse, dependence, and withdrawal resulting from use of oral zolpidem tartrate have been received.

10 OVERDOSAGE

10.1 Signs and Symptoms

In post-marketing experience of overdose with oral zolpidem tartrate alone, or in combination with CNS-depressant agents, impairment of consciousness ranging from somnolence to coma, cardiovascular and/or respiratory compromise, and fatal outcomes have been reported.

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. Zolpidem's sedative-hypnotic effect was shown to be reduced by flumazenil and therefore flumazenil may be useful; however, flumazenil administration may contribute to the appearance of neurological symptoms (convulsions). 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 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.

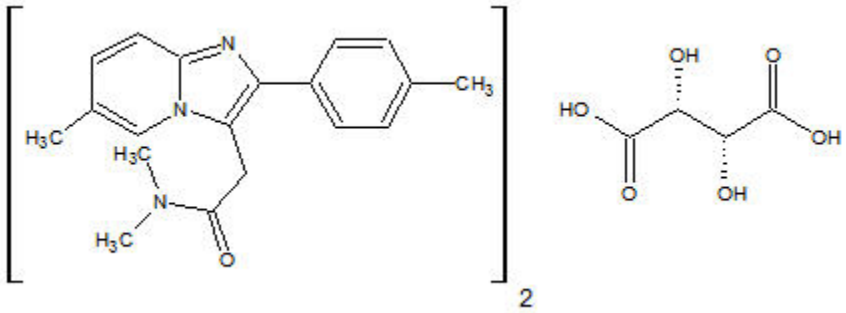
As with management of all overdosage, the possibility of multiple drug ingestion should be considered. The healthcare provider may wish to consider contacting a poison control center for up-to-date information on the management of hypnotic drug overdosage.

11 DESCRIPTION

Intermezzo contains zolpidem tartrate, a non-benzodiazepine hypnotic of the imidazopyridine class. Intermezzo is available in 1.75 mg and 3.5 mg strength tablets for sublingual administration. Intermezzo sublingual tablets are intended to be placed under the tongue where they will disintegrate.

Intermezzo sublingual tablets contain a bicarbonate-carbonate buffer.

Chemically, zolpidem tartrate is *N*,*N*-6-trimethyl-2-*p*-tolylimidazo[1,2-α]pyridine-3-acetamide L-(+)-tartrate (2:1).



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 Intermezzo tablet includes the following inactive ingredients: mannitol, sorbitol, crospovidone, silicon dioxide, sodium carbonate, sodium bicarbonate, croscarmellose sodium, sodium stearyl fumarate, silicon dioxide, natural and artificial spearmint flavor, silicon dioxide-colloidal, and sucralose. The 1.75 mg tablet also contains yellow iron oxide, and the 3.5 mg tablet contains beige iron oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Zolpidem, the active moiety of zolpidem tartrate, 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 complex and shares some of the pharmacological properties of the benzodiazepines. In contrast to the benzodiazepines, which nonselectively bind to and activate all BZ receptor subtypes, zolpidem *in vitro* binds the BZ_1 receptor preferentially with a high affinity ratio of the $alpha_1$/$alpha_5$ subunits. This selective binding of zolpidem on the BZ_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

Absorption

Intermezzo disintegrates in the sublingual cavity after administration. On average, Intermezzo is rapidly absorbed in both genders, with a mean T_{max} across studies of about 35 minutes to about 75 minutes.

In healthy normal volunteers (age 21 to 45 years) dosed with 3.5 mg Intermezzo, the average C_{max} and AUC were 77 ng/mL and 296 ng•h/mL, respectively in women. The average C_{max} and AUC were 53 ng/mL and 198 ng•h/mL, respectively in men. In women, the average C_{max} and AUC of the 1.75 mg Intermezzo dose were 37 ng/mL and 151 ng•h/mL, respectively.

Food decreased the overall C_{max} and AUC of Intermezzo 3.5 mg by 42% and 19%, respectively, and increased the time to peak exposure (T_{max}) to nearly 3 hours. For optimal effect, Intermezzo should not be administered with or immediately after a meal.

Distribution

Based on data obtained with oral zolpidem, the total protein binding was found to be 93% ± 0.1% and remained constant independent of concentration between 40 ng/mL and 790 ng/mL.

Metabolism

Based on data obtained with oral zolpidem, zolpidem tartrate is converted to inactive metabolites that are eliminated primarily by renal excretion.

Elimination

The elimination half-life of a single dose of a 3.5 mg Intermezzo sublingual tablet is approximately 2.5 hours (range 1.4 to 3.6 hours).

Special Populations

Elderly: The recommended dose for Intermezzo is 1.75 mg. A pharmacokinetic study of 1.75 mg and 3.5 mg doses of Intermezzo showed that the plasma C_{max} and $AUC_{0\text{-}4\ hr}$ in elderly subjects following the 3.5 mg dose was higher by 34% and 30%, respectively, than the non-elderly subjects. The C_{max} and AUC of 1.75 mg in elderly subjects were consistently lower than those observed for the 3.5 mg dose in non-elderly subjects but consistently higher than the 1.75 mg dose in non-elderly subjects. The elimination half-life remained unchanged.

Hepatic Impairment: The pharmacokinetics of oral zolpidem tartrate in eight patients with chronic hepatic insufficiency were compared to results in subjects with normal hepatic function. Following a single 20 mg oral zolpidem tartrate dose, mean C_{max} and AUC were found to be two times (250 ng/mL vs. 499 ng/mL) and five times (788 ng•hr/mL vs. 4203 ng•hr/mL) higher, respectively, in hepatically compromised patients compared to subjects with normal hepatic function. 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 subjects with normal hepatic function of 2.2 hr (range: 1.6 to 2.4 hr). Dosing should be modified accordingly in patients with hepatic insufficiency *[see Dosage and Administration (2.5)]*.

Renal Impairment: 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 tartrate 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. Zolpidem was not hemodialyzable. No accumulation of unchanged drug appeared after 14 or 21 days. Zolpidem pharmacokinetics were not significantly different in renally-impaired patients. No dosage adjustment is necessary in patients with renal impairment.

Drug Interactions

CNS-depressants

Co-administration of zolpidem with other CNS depressants increases the risk of CNS depression *[see Warnings and Precautions (5.1)]*. Zolpidem tartrate was evaluated in healthy

volunteers in single-dose interaction studies for several CNS drugs. Imipramine in combination with zolpidem produced no pharmacokinetic interaction other than a 20% decrease in peak levels of imipramine, but there was an additive effect of decreased alertness. Similarly, chlorpromazine in combination with zolpidem produced no pharmacokinetic interaction, but there was an additive effect of decreased alertness and psychomotor performance.

A study involving haloperidol and zolpidem revealed no effect of haloperidol on the pharmacokinetics or pharmacodynamics of zolpidem. The lack of a drug interaction following single-dose administration does not predict the absence of an effect following chronic administration.

An additive adverse effect on psychomotor performance between alcohol and oral zolpidem was demonstrated *[see Warnings and Precautions (5.1)]*.

Following five consecutive nightly doses at bedtime of oral zolpidem tartrate 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.

A single-dose interaction study with zolpidem tartrate 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 were given at steady state and the concentrations evaluated in healthy females, an increase in the zolpidem half-life (17%) was observed. There was no evidence of an additive effect in psychomotor performance.

Drugs that Affect Drug Metabolism via Cytochrome P450

Some compounds known to inhibit CYP3A may increase exposure to zolpidem. The effect of inhibitors of other P450 enzymes on the pharmacokinetics of zolpidem is unknown.

A single-dose interaction study with zolpidem tartrate 10 mg and itraconazole 200 mg at steady-state levels in male volunteers resulted in a 34% increase in $AUC_{0-\infty}$ of zolpidem tartrate. There were no pharmacodynamic effects of zolpidem detected on subjective drowsiness, postural sway, or psychomotor performance.

A single-dose interaction study with zolpidem tartrate 10 mg and rifampin 600 mg at steady-state levels in female subjects 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 tartrate. Rifampin, a CYP3A4 inducer, significantly reduced the exposure to and the pharmacodynamic effects of zolpidem.

A single-dose interaction study with zolpidem tartrate 5 mg and ketoconazole, a potent CYP3A4 inhibitor, given as 200 mg twice daily for 2 days increased C_{max} of zolpidem (30%) and the total AUC of zolpidem (70%) compared to zolpidem alone and prolonged the elimination half-life (30%) along with an increase in the pharmacodynamic effects of zolpidem. Consideration should be given to using a lower dose of zolpidem when ketoconazole and zolpidem are given together.

Other Drugs with No Interactions with Zolpidem

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

Zolpidem tartrate had no effect on digoxin pharmacokinetics and did not affect prothrombin time when given with warfarin in healthy subjects.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Zolpidem was administered in the diet to rats and mice for 2 years at doses of 4, 18, and 80 mg base/kg/day. In mice, these doses are approximately 7, 30, and 140 times, respectively, the recommended human dose (RHD) of 3.5 mg/day (approximately 2.8 mg zolpidem base) on a mg/m^2 basis. In rats, these doses are approximately 15, 60, and 280 times, respectively, the RHD on a mg/m^2 basis. No evidence of carcinogenic potential was observed in mice. In rats, renal tumors (lipoma, liposarcoma) were seen at the mid- and high doses.

Mutagenesis: Zolpidem was negative in *in vitro* (bacterial reverse mutation, mouse lymphoma, and chromosomal aberration) and *in vivo* (mouse micronucleus) genetic toxicology assays.

Impairment of fertility: Oral administration of zolpidem (doses of 4, 20, and 100 mg base/kg/day) to rats prior to and during mating, and continuing in females through postpartum day 25, resulted in irregular estrus cycles and prolonged precoital intervals at the highest dose tested. The no-effect dose for these findings is approximately 70 times the RHD on a mg/m^2 basis. There was no impairment of fertility at any dose tested.

14 CLINICAL STUDIES

14.1 Middle-of-the-Night Awakening Trials

Intermezzo was evaluated in two randomized, double-blind, placebo-controlled studies (Studies 1 and 2) in patients with insomnia characterized by difficulty returning to sleep after a middle-of-the-night (MOTN) awakening. In these studies, patients met the diagnosis for primary insomnia as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) and had at least three prolonged MOTN awakenings per week that were at least 30 minutes in duration.

Sleep Laboratory Study (Scheduled Dosing)

Adult patients aged 19 to 64 years (N=82; 58 female, 24 male) with a history of difficulty returning to sleep after middle-of-the-night awakenings were evaluated in a double-blind, placebo-controlled, 3-period cross-over sleep laboratory study (Study 1). The primary outcome measure was latency to persistent sleep (LPS).

Doses of 3.5 mg and 1.75 mg of Intermezzo significantly decreased both objective (by polysomnography) and subjective (patient-estimated) sleep latency after a scheduled middle-of-the-night awakening as compared to placebo. The effect on sleep latency was similar for females receiving 1.75 mg of Intermezzo and males receiving 3.5 mg of Intermezzo.

Outpatient Study (As-needed Dosing)

Adult patients aged 18 to 64 years (N=295; 201 women, 94 men) with difficulty returning to sleep after middle-of-the-night awakenings were evaluated in a double-blind, placebo-controlled 4-week outpatient study of Intermezzo. Patients took study drug (3.5 mg of Intermezzo or placebo) on an as-needed (prn) basis, when they had difficulty returning to sleep

after waking in the middle of the night, provided they had at least 4 hours time remaining in bed. Subjective (patient-estimated) time to fall back to sleep after middle-of-the-night awakening was significantly shorter for Intermezzo 3.5 mg compared to placebo.

14.2 Special Safety Studies

Driving Study

A randomized, double-blind, placebo-controlled, active-control, single-center, four-period, crossover study in 40 healthy subjects was conducted to evaluate the effects of middle-of-the-night administration of Intermezzo on next-morning driving performance. The four randomized treatments included Intermezzo 3.5 mg four hours before driving, Intermezzo 3.5 mg three hours before driving, placebo, and a positive control (an unapproved sedative-hypnotic) given nine hours before driving.

The primary outcome measure was the change in the standard deviation of lateral position (SDLP), a measure of driving impairment. The results were analyzed using a symmetry analysis, which determined the proportion of subjects whose change from their own SDLP in the placebo condition was statistically significantly above a threshold thought to reflect clinically meaningful driving impairment.

When driving began 3 hours after taking Intermezzo, testing had to be terminated for one subject (a 23-year old woman) due to somnolence. Overall, the symmetry analysis showed a statistically significant impairing effect at 3 hours. When driving began 4 hours after taking Intermezzo, statistically significant impairment was not found, but numerically Intermezzo was worse than placebo. Zolpidem blood levels were not measured in the driving study, and the study was not designed to correlate specific blood level with degree of impairment. However, the estimated blood level of zolpidem in patients whose SDLP worsened according to the symmetry analysis is considered to present a risk for driving impairment. In some women, the 3.5 mg dose of Intermezzo results in zolpidem blood levels that remain at or sometimes considerably above this level 4 or more hours after dosing. Therefore, the recommended dose for women is 1.75 mg. A small negative effect on SDLP may remain in some patients 4 hours after the 1.75 mg dose in women, and after the 3.5 mg dose in men, such that a potential negative effect on driving cannot be completely excluded.

Rebound effects

In studies performed with other zolpidem formulations (5 mg to 10 mg oral zolpidem tartrate) given at bedtime, there was no objective (polysomnographic) evidence of rebound insomnia at recommended doses seen in studies evaluating sleep on the nights following discontinuation. 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 oral zolpidem tartrate.

Memory impairment in controlled studies

Controlled studies in adults utilizing objective measures of memory yielded no consistent evidence of next-day memory impairment following the administration at bedtime of 5 mg to 10 mg oral zolpidem tartrate. However, in one study involving zolpidem tartrate doses of 10 mg 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 oral zolpidem tartrate, predominantly at doses above 10 mg.

16 HOW SUPPLIED/STORAGE AND HANDLING

Each sublingual tablet is individually packaged in a foil blister inside a unit-dose pouch.

Intermezzo 1.75 mg tablets are yellow, round, uncoated, biconvex, debossed with ZZ on one side and supplied as:

NDC 59011-256-30: Carton of 30 unit-dose pouches

Intermezzo 3.5 mg tablets are beige, round, uncoated, biconvex, debossed with ZZ on one side and supplied as:

NDC 59011-255-30: Carton of 30 unit-dose pouches

Storage and Handling

Store between 20°C to 25°C (68°F to 77°F). Excursions permitted between 15°C and 30°C (59°F and 86°F). Protect from moisture.

The patient should be instructed not to remove the blister from the unit-dose pouch until the patient is ready to consume the sublingual tablet inside.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

Inform patients and their families about the benefits and risks of treatment with Intermezzo. Inform patients of the availability of a Medication Guide and instruct them to read the Medication Guide prior to initiating treatment with Intermezzo and with each prescription refill. Review the Intermezzo Medication Guide with every patient prior to initiation of treatment. Instruct patients or caregivers that Intermezzo should be taken only as prescribed.

CNS depressant Effects and Next-Day Impairment

Tell patients that Intermezzo has the potential to cause next-day impairment, and that this risk is increased if dosing instructions are not carefully followed. Tell patients to wait for at least 4 hours after dosing and until they feel fully awake before driving or engaging in other activities requiring full mental alertness.

Severe Anaphylactic and Anaphylactoid Reactions

Inform patients that severe anaphylactic and anaphylactoid reactions have occurred with zolpidem. Describe the signs/symptoms of these reactions and advise patients to seek medical attention immediately if any of them occur.

Sleep-driving and Other Complex Behaviors

Instruct patients to inform their families that zolpidem has been associated with “sleep-driving” and other complex behaviors while not being fully awake (preparing and eating food, making phone calls, or having sex), and tell patients and their families to call their healthcare providers immediately if they develop any of these symptoms.

Suicide

Tell patients to immediately report any suicidal thoughts.

Administration Instructions

For detailed instructions on how to use Intermezzo, tell patients to refer to the Patient Instructions for Use.

Tell patients that Intermezzo is to be taken only once per night if needed if they wake in the middle of the night and have difficulty returning to sleep. Tell patients that Intermezzo should only be taken if they have 4 hours of bedtime remaining before the planned time of waking.

Instruct the patient to place the tablet under the tongue, allowing it to disintegrate completely before swallowing. Tell the patient that Intermezzo should not be swallowed whole.

Tell patients that the effect of Intermezzo may be slowed if taken with or immediately after a meal.

Instruct patients to remove the blister from the unit-dose pouch just prior to dosing.

Advise patients NOT to take Intermezzo if they drank alcohol that day or before bed.

Healthcare professionals can telephone Purdue Pharma's Medical Services Department (1-888-726-7535) for information on this product.

Distributed by:
Purdue Pharma L.P.
Stamford, CT 06901-3431
Manufactured by: Patheon Pharmaceuticals, Inc., Cincinnati, OH 45237

MEDICATION GUIDE

Intermezzo® (in ter mét zoh)

(zolpidem tartrate) sublingual tablet CIV

Read the Medication Guide that comes with Intermezzo® before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your doctor about your medical condition or treatment.

What is the most important information I should know about Intermezzo?

Follow the Instructions for Use at the end of this Medication Guide when you take Intermezzo. If you do not follow the Instructions for Use, you might be drowsy in the morning without knowing it.

- **Only take one tablet a night, if needed.**
- **Only take Intermezzo if you have at least 4 hours of bedtime left.**

Intermezzo may cause serious side effects, including:

- **After taking Intermezzo, you may get up out of bed while not being fully awake and do an activity that you do not know you are doing. The next morning, you may not remember that you did anything during the night.** You have a higher chance for doing these activities if you drank alcohol that day or take other medicines that make you sleepy with Intermezzo. Reported activities include:

- driving a car ("sleep-driving")
- making and eating food
- talking on the phone
- having sex
- sleep-walking

Call your healthcare provider right away if you find out that you have done any of the above activities after taking Intermezzo.

Important:

1. **Take Intermezzo exactly as prescribed**
2. **Do not take Intermezzo if you:**
   - drank alcohol that day or before bed.
   - took another medicine to help you sleep.
   - do not have at least 4 hours of bedtime remaining.

What is Intermezzo?

Intermezzo is a sedative-hypnotic (sleep) medicine. Intermezzo is used in adults for the treatment of a sleep problem called insomnia. Many people have difficulty returning to sleep after awakening in the middle of the night. Intermezzo is designed to specifically treat this problem.

It is not known if Intermezzo is safe and effective in children.

Intermezzo is a federally controlled substance (CIV) because it can be abused or lead to dependence. Keep Intermezzo in a safe place to prevent misuse and abuse. Selling or giving away Intermezzo may harm others, and is against the law. Tell your doctor if you have ever abused or have been dependent on alcohol, prescription medicines, or street drugs.

Who should not take Intermezzo?

- Do not take Intermezzo if you are allergic to zolpidem or any other ingredients in Intermezzo. See the end of this Medication Guide for a complete list of ingredients in Intermezzo.
- Do not take Intermezzo if you have had an allergic reaction to drugs containing zolpidem, such as Ambien, Ambien CR, Edluar, or Zolpimist.

Symptoms of a serious allergic reaction to Intermezzo can include:

- **swelling of your face, lips, and throat that may cause difficulty breathing or swallowing**
- **nausea and vomiting**

Intermezzo may not be right for you. Before starting Intermezzo, tell your doctor about all of your health conditions, including if you:

- have a history of depression, mental illness, or suicidal thoughts
- have a history of drug or alcohol abuse or addiction

- have kidney or liver disease
- have a lung disease or breathing problems
- are pregnant, planning to become pregnant, or breastfeeding

Tell your doctor about all of the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements. Medicines can interact with each other, sometimes causing serious side effects. Your doctor will tell you if you can take Intermezzo with your other medicines.

Know the medicines you take. Keep a list of your medicines with you to show your doctor and pharmacist each time you get a new medicine.

How should I take Intermezzo?

- See **"What is the most important information I should know about Intermezzo"**
- Read the **"Instructions for Use"** at the end of this Medication Guide for detailed instructions on how to take Intermezzo.
- Take Intermezzo exactly as prescribed. Only take one Intermezzo tablet per night if needed.
- Do not take Intermezzo if you drank alcohol that evening or before bed.
- While in bed, place the tablet under your tongue and allow it to break apart completely. Do not swallow it whole.
- You should not take Intermezzo with or right after a meal. Intermezzo may help you fall asleep faster when you take it on an empty stomach.
- Call your health care provider if your insomnia worsens or is not better within 7 to 10 days. This may mean that there is another condition causing your sleep problem.
- If you take too much Intermezzo or overdose get emergency treatment.

What are the possible side effects of Intermezzo?

Intermezzo may cause serious side effects, including:

- **getting out of bed while not being fully awake and doing an activity that you do not know you are doing.** (See **"What is the most important information I should know about Intermezzo?"**)
- **abnormal thoughts and behavior.** Symptoms include more outgoing or aggressive behavior than normal, confusion, agitation, hallucinations, worsening of depression, and suicidal thoughts or actions.
- **memory loss**
- **anxiety**
- **severe allergic reactions.** Symptoms include swelling of the tongue or throat, trouble breathing, and nausea and vomiting. Get emergency medical help if you get these symptoms after taking Intermezzo.

Call your health care provider right away if you have any of the above side effects or any other side effects that worry you while using Intermezzo.

The most common side effects of Intermezzo are:

- Headache
- Nausea
- Fatigue

Even if you follow the Instructions for Use, you may still feel drowsy in the morning after taking Intermezzo. Do not drive or do other dangerous activities after taking Intermezzo until you are fully awake.

These are not all the side effects of Intermezzo. Ask your health care provider or pharmacist for more information.

You may report side effects to FDA at 1-800-FDA-1088.

How should I store Intermezzo?

- Store Intermezzo at room temperature, 68° to 77°F (20° to 25°C). Protect from moisture.
- Only open the pouch when you are ready to use Intermezzo.

Keep Intermezzo and all medicines out of reach of children.

General Information about Intermezzo

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Intermezzo for a condition for which it was not prescribed. Do not give Intermezzo to other people, even if you think they have the same symptoms that you have. It may harm them and it is against the law.

This Medication Guide summarizes the most important information about Intermezzo. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about Intermezzo that is written for healthcare professionals. For more information about Intermezzo, call Purdue Pharma at 1-888-726-7535 or go to www.purduepharma.com or www.intermezzorx.com.

What are the ingredients in Intermezzo?

Active Ingredient: Zolpidem tartrate

Inactive Ingredients: Each Intermezzo tablet includes the following inactive ingredients: mannitol, sorbitol, crospovidone, silicon dioxide, sodium carbonate, sodium bicarbonate, croscarmellose sodium, sodium stearyl fumarate, silicon dioxide, natural and artificial spearmint flavor, silicon dioxide-colloidal, and sucralose. The 1.75 mg tablet also contains yellow iron oxide, and the 3.5 mg tablet contains beige iron oxide.

Rx only

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Distributed by:
Purdue Pharma L.P.
Stamford, CT 06901-3431

Issued: July 2012

Instructions for Use
Intermezzo® (in ter mét zoh)
(zolpidem tartrate) sublingual tablet CIV

Read these Instructions for Use before you start taking Intermezzo and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is the most important Information I should know about Intermezzo?

Follow these Instructions for Use when you take Intermezzo. If you do not follow these instructions, you might be drowsy in the morning without knowing it.

- Only take 1 tablet a night if needed
- Only take Intermezzo if you have at least 4 hours of bedtime left

Using Intermezzo the wrong way can make you drowsy in the morning.

Before you go to bed:

- Place only 1 Intermezzo pouch by your bed, and have a clock or watch nearby (see Figure A).

Figure A

- Store all other unopened Intermezzo pouches with your other medicines away from your bedside.
- Only open the Intermezzo pouch when you are ready to use it.
- You can either use the **Intermezzo Dosing Time Chart** (see Figure B) or the **Dosing Time Tool** (see Figure C) that comes with Intermezzo to find the latest time during the night you can take Intermezzo.

Intermezzo Dosing Time Chart (see Figure B):

- You can take Intermezzo if you have at least 4 hours of bedtime left before you must be awake.
- Find the earliest time you have to be up and awake in the column on the left.

- Find the latest time you can take Intermezzo on the same line in the column on the right.

Intermezzo Dosing Time Chart

If you must be awake by:	Take Intermezzo before:
4 am	12 midnight
5 am	1 am
6 am	2 am
7 am	3 am
8 am	4 am
9 am	5 am

Figure B

Intermezzo Dosing Time Tool (see Figure C):

- Turn the Intermezzo Dosing Time Tool wheel to show the earliest time that you must be awake under the green arrow.
- Take Intermezzo before the time under the brown arrow.

Figure C

During the night when you take Intermezzo:

Step 1. Check the current time and use the Intermezzo Dosing Time Chart or the Intermezzo Dosing Time Tool to decide if you should take Intermezzo.

- Only take Intermezzo if you have at least 4 hours of bedtime left before you have to be awake (see Figure B).

Step 2. Open the Intermezzo pouch you placed by your bed.

- Fold the Intermezzo pouch along the dotted line. While the Intermezzo pouch is folded, tear the pouch open at the notch at the center of the dotted line (see Figure D).

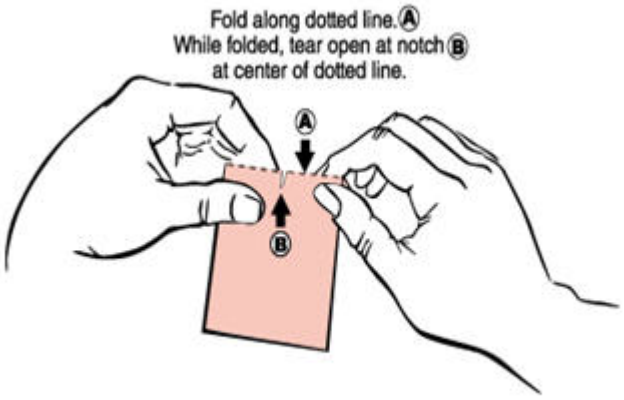


Figure D

Step 3. Remove the foil blister from the Intermezzo pouch. Push the Intermezzo tablet through the foil (see Figure E).

Figure E

Step 4. Leave the empty Intermezzo pouch where you can see it. The empty pouch will help remind you that you already took your Intermezzo dose (see Figure F).

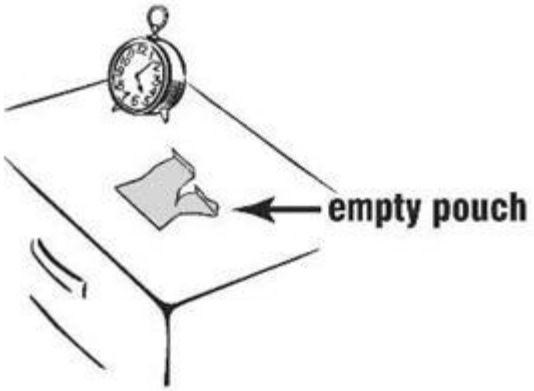


Figure F

Step 5. While in bed, place the Intermezzo tablet under your tongue and allow it to break apart completely, then swallow. Do not swallow it whole (see Figure G).

Figure G

Step 6. Throw the empty Intermezzo pouch away in the morning.

When you wake up in the morning, be sure that at least 4 hours have passed since you have taken Intermezzo and you feel fully awake before driving. Do not do dangerous activities until you know how Intermezzo affects you.

This Medication Guide and Instructions for Use have been approved by the U.S. Food and Drug Administration.

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EXHIBIT B

US008242131B2

(12) **United States Patent**
Singh et al.

(10) **Patent No.: US 8,242,131 B2**
(45) **Date of Patent: Aug. 14, 2012**

(54) **METHODS OF TREATING MIDDLE-OF-THE-NIGHT INSOMNIA**

(75) Inventors: **Nikhilesh Singh**, Mill Valley, CA (US); **Sathasivan Indiran Pather**, Greenbrae, CA (US)

(73) Assignee: **Transcept Pharmaceuticals, Inc.**, Pt. Richmond, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 1185 days.

(21) Appl. No.: **11/439,874**

(22) Filed: **May 23, 2006**

(65) **Prior Publication Data**

US 2007/0066643 A1 Mar. 22, 2007

Related U.S. Application Data

(60) Provisional application No. 60/684,842, filed on May 25, 2005, provisional application No. 60/741,673, filed on Dec. 1, 2005, provisional application No. 60/788,340, filed on Mar. 31, 2006, provisional application No. 60/788,249, filed on Mar. 31, 2006.

(51) **Int. Cl.**
A61K 31/44 (2006.01)

(52) **U.S. Cl.** **514/294**; 514/923

(58) **Field of Classification Search** 514/294, 514/923

See application file for complete search history.

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(57) **ABSTRACT**

The present invention provides compositions and methods for treating middle-of-the-night insomnia without residual sedative effects upon awakening by administering low doses (about 5 mg or less) of zolpidem or a salt thereof.

25 Claims, 7 Drawing Sheets

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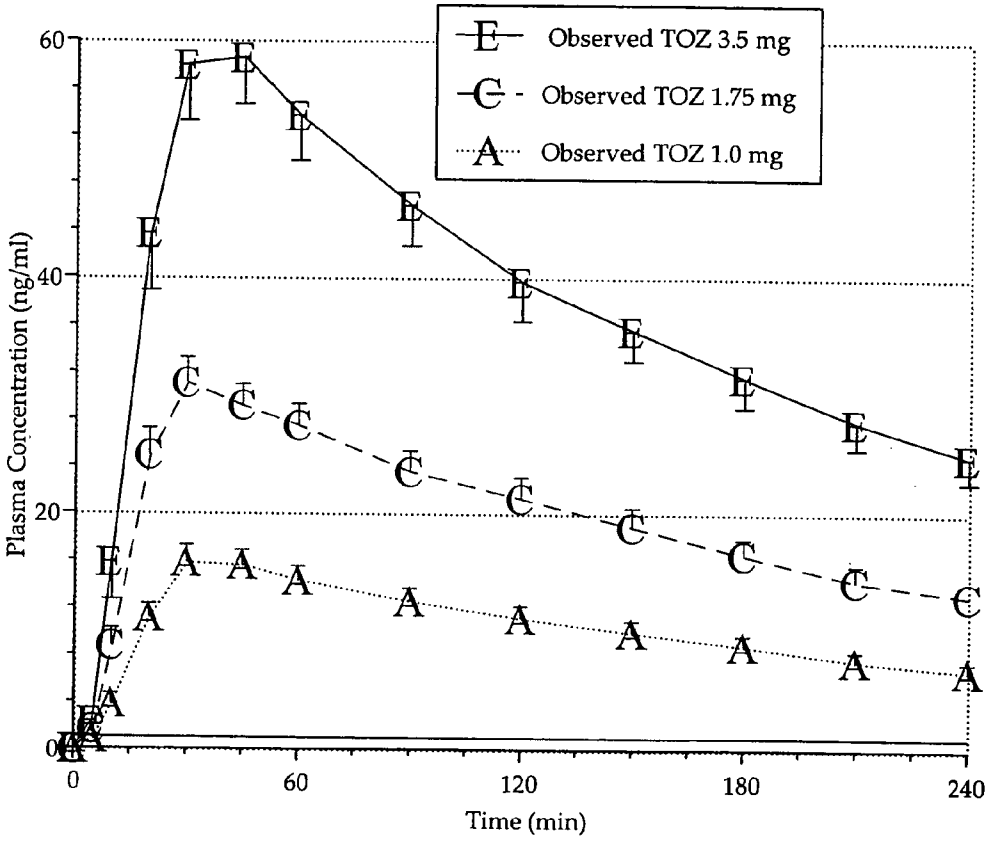
Observed TOZ 3.5 mg
Observed TOZ 1.75 mg
Observed TOZ 1.0 mg
Plasma Concentration (ng/ml)
60
40
20
0
0
60
120
180
240
Time (min)

FIG. 1

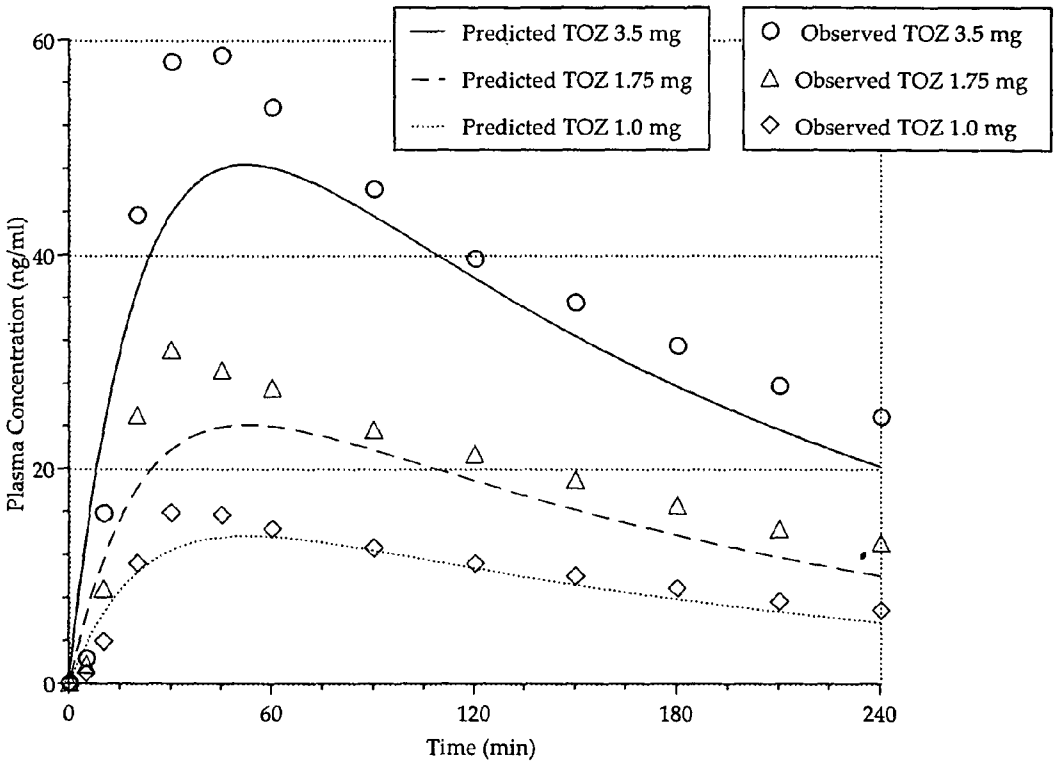
Predicted TOZ 3.5 mg
Predicted TOZ 1.75 mg
Predicted TOZ 1.0 mg
Observed TOZ 3.5 mg
Observed TOZ 1.75 mg
Observed TOZ 1.0 mg
Plasma Concentration (ng/ml)
60
40
20
0
0
60
120
180
240
Time (min)

FIG. 2

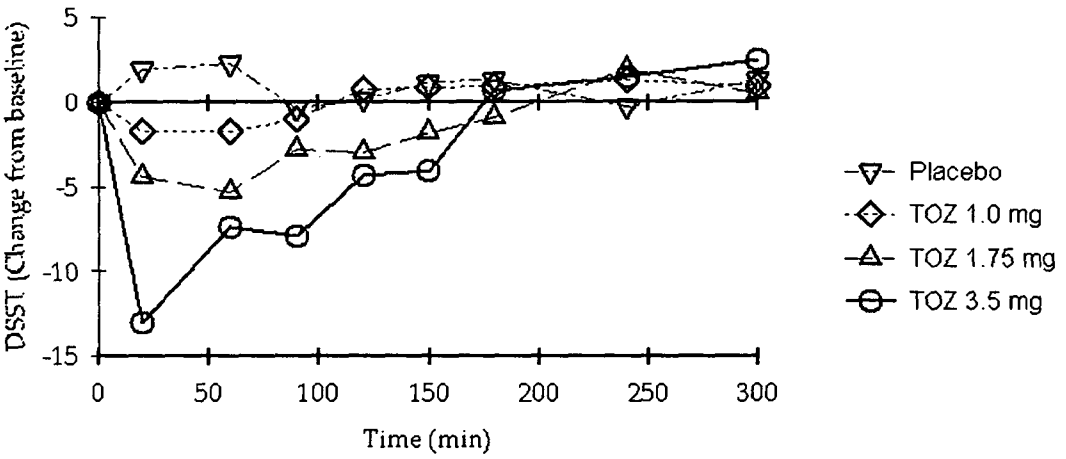
DSST (Change from baseline)
5
0
-5
-10
-15
0
50
100
150
200
250
300
Time (min)
Placebo
TOZ 1.0 mg
TOZ 1.75 mg
TOZ 3.5 mg

FIG. 3

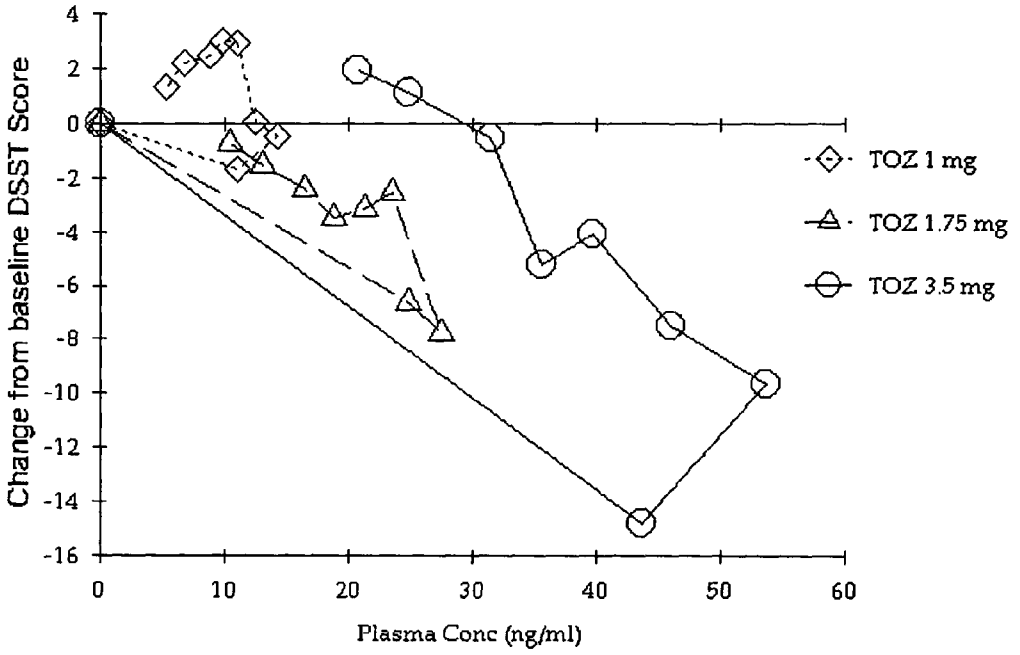
Change from baseline DSST Score
4
2
0
-2
-4
-6
-8
-10
-12
-14
-16
0
10
20
30
40
50
60
Plasma Conc (ng/ml)
TOZ 1 mg
TOZ 1.75 mg
TOZ 3.5 mg

FIG. 4

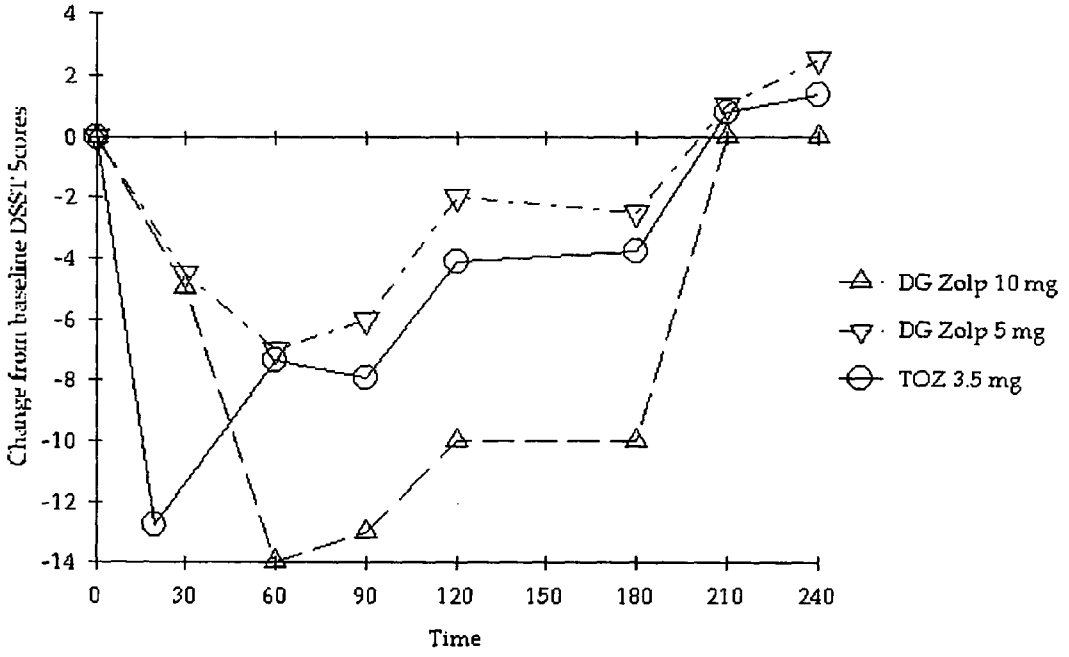
Change from baseline DSST Scores
4
2
0
-2
-4
-6
-8
-10
-12
-14
0
30
60
90
120
150
180
210
240
Time
DG Zolp 10 mg
DG Zolp 5 mg
TOZ 3.5 mg

FIG. 5

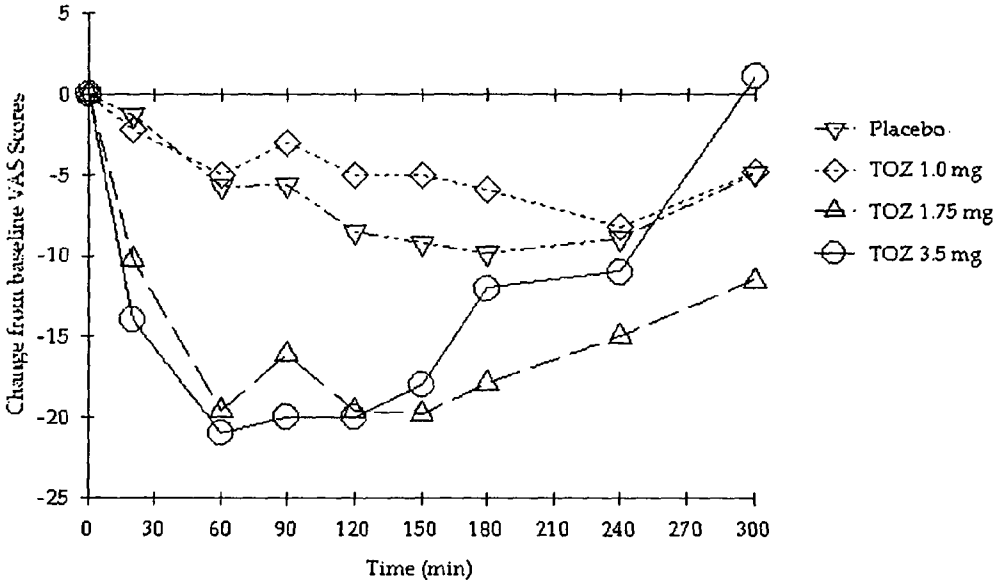
5
0
-5
-10
-15
-20
-25
Change from baseline VAS Scores
0
30
60
90
120
150
180
210
240
270
300
Time (min)
Placebo
TOZ 1.0 mg
TOZ 1.75 mg
TOZ 3.5 mg

FIG. 6

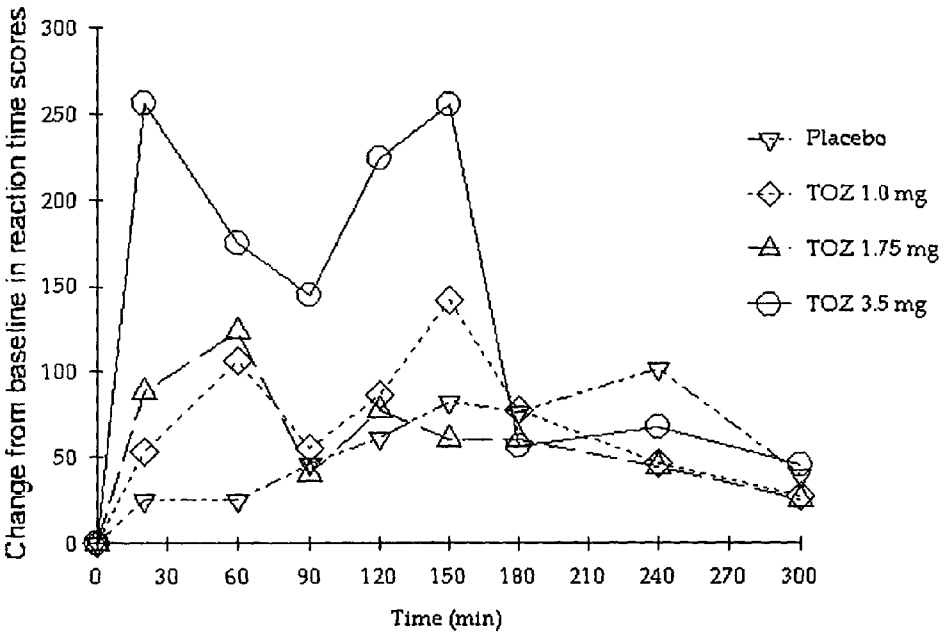
Change from baseline in reaction time scores
300
250
200
150
100
50
0
0
30
60
90
120
150
180
210
240
270
300
Time (min)
Placebo
TOZ 1.0 mg
TOZ 1.75 mg
TOZ 3.5 mg

FIG. 7

METHODS OF TREATING MIDDLE-OF-THE-NIGHT INSOMNIA

CROSS-REFERENCES TO RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application No. 60/684,842, filed May 25, 2005, U.S. Provisional Application No. 60/741,673, filed Dec. 1, 2005, U.S. Provisional Application No. 60/788,340, filed Mar. 31, 2006, and U.S. Provisional Application No. 60/788,249, filed Mar. 31, 2006, the disclosures of which are hereby incorporated by reference in their entirety for all purposes.

BACKGROUND OF THE INVENTION

Until recently, medical literature has recognized four types of insomnia, including sleep onset insomnia (e.g., trouble falling asleep at bedtime), sleep maintenance insomnia (e.g., disturbed sleep during the night), early morning awakening, and transient insomnia (e.g., new environment, first night in hotel syndrome). However, according to the National Sleep Foundation's 2005 "Sleep in America" poll, about 20% of total respondents and about 50% of respondents reporting insomnia symptoms complained of waking up too early and having difficulty returning to sleep at least a few nights a week (results available on the worldwide web at sleepfoundation-.org). This type of insomnia includes "middle-of-the-night" insomnia, "late night" insomnia, "prolonged awakening after sleep onset" insomnia, "sleep maintenance" insomnia, and insomnia that follows after "middle-of-the-night" awakening, each of which has a component of interrupted sleep.

More particularly, patients with "middle-of-the-night" (MOTN) insomnia generally do not have problems initially falling asleep, but wake up prior to their intended wake time (during their normal sleep time), usually with about 3 to 4 hours of sleep time remaining. These patients require a treatment intervention that would reduce their wake time during their sleep time after awakening without leaving residual sedative effects in the morning. Unfortunately, currently available hypnotic medications are unsuitable for treating MOTN insomnia because they are slow to induce sleep (e.g., zaleplon) and/or require administration prior to about 7 to 9 hours in bed to avoid residual sleepiness in the morning (e.g., available dosage forms of zolpidem, eszopiclone, and zopiclone). Also, administration of most presently available hypnotics is prophylactic, resulting in unnecessary medication and overmedication of persons who require treatment for their MOTN insomnia a few nights a week.

Clearly, there remains a need for appropriate treatments for persons with MOTN insomnia. The present invention fulfills this and other needs.

BRIEF SUMMARY OF THE INVENTION

The present invention provides compositions and methods for treating MOTN insomnia with zolpidem or a salt thereof.

In one aspect, the present invention provides a solid unit dosage composition for the treatment of MOTN insomnia, the composition comprising an effective amount of zolpidem or a salt thereof, formulated for delivery of zolpidem across a subject's oral mucosa, wherein the effective amount is an amount of less than 1.30×10^{-5} moles of zolpidem, and is an amount sufficient to produce a plasma concentration between about 25 ng/ml and about 50 ng/ml within 20 minutes of administration, when evaluated in an appropriate patient population.

In another aspect, the present invention provides a solid unit dosage composition for the treatment of MOTN insomnia, the composition comprising an amount of zolpidem or a salt thereof effective to produce sleep within 30 minutes of dosing a subject, but does not produce residual sedative effects when the subject is awakened at a time about 4 hours after dosing, when the composition is evaluated in an appropriate patient population.

In yet another aspect, the present invention provides a pharmaceutical composition suitable for absorption by the oral mucosa in the treatment of MOTN insomnia, the composition comprising from about 0.5 mg to about 4.0 mg of zolpidem or a salt thereof and a pharmaceutically acceptable excipient.

In a further aspect, the present invention provides a solid pharmaceutical composition for delivery across the oral mucosa for treating insomnia comprising zolpidem in an amount less than 5 mg and a buffer.

In a related aspect, the present invention provides a solid pharmaceutical composition for delivery across the oral mucosa for treating insomnia comprising zolpidem in an amount less than 5 mg and a binary buffer.

In another related aspect, the present invention provides a solid unit dosage pharmaceutical composition comprising a dose of zolpidem hemitartrate in an amount of less than 5 mg and a binary buffer system capable of raising the pH of a subject's saliva to a pH greater than about 8.5, irrespective of the starting pH of saliva, wherein the composition is formulated for delivery of zolpidem across the subject's oral mucosa.

In an additional aspect, the present invention provides a pharmaceutical composition for treating insomnia comprising zolpidem in an amount less than 5 mg and a binary buffer.

In a related aspect, the present invention provides a pharmaceutical composition for treating insomnia comprising zolpidem in an amount less than 5 mg and a binary buffer, wherein the composition is formulated for delivery of zolpidem across the oral mucosa and the binary buffer produces a saliva pH of at least 8.5, irrespective of the starting saliva pH.

In another aspect, the present invention provides a method of treating insomnia, the method comprising:

administering to a subject who awakens from sleep and desires to return to sleep within 30 minutes and sleep for less than 5 hours, a single unit dosage composition comprising an effective amount of zolpidem or a salt thereof, formulated for delivery of zolpidem across the subject's oral mucosa,

wherein the effective amount is an amount of less than 1.30×10^{-5} moles of zolpidem, and is an amount sufficient to produce a plasma concentration between about 25 ng/ml and about 50 ng/ml within 20 minutes of administration, when evaluated in an appropriate patient population.

In a related aspect, the present invention provides a method of treating MOTN insomnia in a subject, the method comprising:

administering to the subject a pharmaceutical composition comprising zolpidem or a salt thereof in an amount of less than 1.30×10^{-5} moles of zolpidem,

wherein the administering is on an as-needed basis, and wherein delivery of zolpidem occurs across the subject's oral mucosa to produce a blood level of zolpidem in the subject between about 25 ng/ml and about 50 ng/ml within about 20 minutes of administration and less than 20 ng/ml at a time 4 hours after administration.

In yet another aspect, the present invention provides a method of treating insomnia in a subject, the method comprising:

administering to the subject a pharmaceutical composition comprising zolpidem or a salt thereof,

wherein the composition provides delivery of zolpidem across the subject's oral mucosa, wherein the subject is a subject who awakens from sleep and desires to resume sleep for less than 5 hours, and wherein the composition produces sleep within 30 minutes of dosing and the dose is such that it does not produce residual sedative effects when the subject is awakened at a time 4 hours after dosing.

In a further aspect, the present invention provides a method of treating insomnia in a subject, the method comprising:

administering a solid pharmaceutical composition comprising zolpidem in an amount less than 5 mg and a buffer, to a subject who awakens from sleep and desires to resume sleep for less than 5 hours,

wherein the solid pharmaceutical composition provides delivery of zolpidem across the subject's oral mucosa, and wherein a blood level of zolpidem is achieved in the subject of between about 25 ng/ml and about 50 ng/ml within about 20 minutes of administration.

In a related aspect, the present invention provides a method of treating insomnia, the method comprising the steps of:

providing a solid pharmaceutical composition comprising zolpidem in an amount less than 5 mg and a buffer to a patient who awakens from sleep and desires to resume sleep for less than 5 hours; and

administering the solid pharmaceutical composition to the patient for delivery of the zolpidem across the patient's oral mucosa,

wherein a blood level of zolpidem in the patient is between about 25 ng/ml and about 50 ng/ml within about 20 minutes of administration.

In an additional aspect, the present invention provides a method of treating insomnia, the method comprising:

administering a solid pharmaceutical composition comprising zolpidem in an amount less than 5 mg and a binary buffer, to a subject who awakens from sleep and desires to resume sleep for less than 5 hours,

wherein the solid pharmaceutical composition provides delivery of zolpidem across the subject's oral mucosa, wherein the solid pharmaceutical composition dissolves or disintegrates in about 2 minutes or less in the subject's mouth, and wherein the binary buffer raises the pH of saliva in the subject's mouth to a pH greater than about 9.0.

In a related aspect, the present invention provides a method of treating insomnia, the method comprising the steps of:

providing a solid pharmaceutical composition comprising zolpidem in an amount less than 5 mg and a binary buffer to a patient who awakens from sleep and desires to resume sleep for less than 5 hours; and

administering the solid pharmaceutical composition to the patient for delivery of the zolpidem across the patient's oral mucosa,

wherein the solid pharmaceutical composition dissolves or disintegrates in about 2 minutes or less in the patient's mouth, and wherein the binary buffer raises the pH of saliva in the patient's mouth to a pH greater than about 9.0.

Other objects, features, and advantages of the present invention will be apparent to one of skill in the art from the following detailed description and figures.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** shows the mean (SEM) plasma concentration time profiles of a 1.0 mg, 1.75 mg, and 3.5 mg sublingual zolpidem lozenge of the present invention.

FIG. **2** shows the predicted versus observed plasma profiles of a 1.0 mg, 1.75 mg, and 3.5 mg sublingual zolpidem lozenge of the present invention.

FIG. **3** shows the Digit Symbol Substitution Test (DSST) scores of a 1.0 mg, 1.75 mg, and 3.5 mg sublingual zolpidem lozenge of the present invention as a function of time.

FIG. **4** shows the DSST scores of a 1.0 mg, 1.75 mg, and 3.5 mg sublingual zolpidem lozenge of the present invention as a function of plasma concentration.

FIG. **5** shows a comparison of DSST scores of a 3.5 mg sublingual zolpidem lozenge of the present invention and 5 mg and 10 mg peroral (PO) Ambien® as reported in the literature.

FIG. **6** shows the Visual Analog Scale (VAS) scores of a 1.0 mg, 1.75 mg, and 3.5 mg sublingual zolpidem lozenge of the present invention.

FIG. **7** shows the change in reaction time scores as measured by a Psychomotor Vigilance Test (PVT) of a 1.0 mg, 1.75 mg, and 3.5 mg sublingual zolpidem lozenge of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

I. General

The present invention provides compositions and methods for treating insomnia, particularly MOTN insomnia, using therapeutically effective low doses of zolpidem or a salt thereof by delivering zolpidem across the oral mucosa. The present invention is based, in part, upon the surprising discovery that low doses of zolpidem, when formulated for delivery across the oral mucosa, can induce rapid onset of sleep without residual sedative effects upon awakening 2-4 hours later. Advantages of taking a low dose amount of zolpidem (e.g., less than 5 mg or 1.30×10^{-5} moles) to counteract MOTN insomnia include rapid action to induce sleep, treatment on an as-needed basis to avoid excessive and unnecessary medication, and no or minimal residual sedative effects upon awakening.

While there are various types of dosage forms, solid dosage forms for oral administration are perhaps among the most preferred by patients, and among the most prevalently used. Many of the dosage forms are medicaments formulated as tablets or capsules, which are swallowed. However, swallowed formulations have several disadvantages, including drug losses during hepatic first pass metabolism, during enzymatic degradation within the gastrointestinal tract, and during absorption to non-targeted tissues. These drug losses not only increase the variability in drug response, but also often require that the medicament be given in greater initial doses. Still further, as the drug has to pass through the gastrointestinal system in order to enter the blood stream, the time to reach a therapeutic effect may be quite long, typically around forty-five minutes or longer.

Drug delivery via the mucous membranes of the oral cavity has certain advantages, due to the properties of the oral mucosa itself. For example, the mucous membranes of the oral cavity are highly vascularized and well supplied with lymphatic drainage sites. In general, the mucous membranes of the oral cavity can be divided into five main regions: the floor of the mouth (sublingual), the cheeks (buccal), the gums (gingival), the roof of the mouth (palatal), and the lining of the lips. These regions differ from each other with respect to their anatomy, drug permeability, and physiological response to drugs. For example, in terms of permeability, sublingual is more permeable than buccal, which is more permeable than palatal. This permeability is generally based on the relative

thickness and degree of keratinization of these membranes, with the sublingual mucosa being relatively thin and non-keratinized, the buccal mucosa being thicker and non-keratinized, and the palatal mucosa being intermediate in thickness, but keratinized.

Accordingly, in certain aspects, the present invention provides solid dosage forms containing low doses of zolpidem (e.g., dissolving tablets, lozenges, etc.) and methods for treating MOTN insomnia by administering such compositions to the oral mucosa to deliver and facilitate absorption of a substantial portion of the dose through the tissues of the buccal and/or sublingual cavity. In some embodiments, the solid dosage forms described herein facilitate buccal and/or sublingual absorption due to the presence of a buffer system (e.g., a bicarbonate/carbonate buffer system). Without being bound to any particular theory, the buffer system can promote the in situ conversion of a hydrophilic (i.e., charged) form of zolpidem (e.g., zolpidem hemitartrate) into its lipophilic free-base (i.e., neutral) form, which penetrates the lipid membranes in the oral mucosa more readily than the salt form. As a result, both non-elderly and elderly patients can benefit from taking a substantially lower dose of zolpidem (e.g., about 3.5 mg for non-elderly; about 1.75 mg for elderly) as compared to the lowest currently approved dose of 5 mg, thereby rapidly inducing sleep without residual sedative effects upon awakening.

It is also desirable to reduce variability in drug delivery. Surprisingly, this can be achieved by utilizing a binary buffer system capable of achieving and sustaining a final pH in the oral cavity, independent of the initial pH. Accordingly, compositions for delivering zolpidem or a salt thereof across the oral mucosa having a buffer system that produces a final pH, independent of the initial pH, and which sustains that final pH for a given period of time, are particularly desirable, and are provided herein.

II. Definitions

As used herein, the following terms have the meanings ascribed to them unless specified otherwise.

The term "sleep disorder" refers to a disruptive pattern of sleep arising from many causes including, without limitation, dysfunctional sleep mechanisms, abnormalities in physiological functions during sleep, abnormalities of the biological clock, and sleep disturbances that are induced by factors extrinsic to the sleep process. In particular, the term encompasses disorders associated with difficulties in staying asleep and/or falling asleep such as insomnia (e.g., transient, short-term, and chronic), delayed sleep phase syndrome, hypnotic-dependent sleep disorder, and stimulant-dependent sleep disorder; disorders associated with difficulties in staying awake such as sleep apnea, narcolepsy, restless leg syndrome, obstructive sleep apnea, central sleep apnea, idiopathic hypersomnia, respiratory muscle weakness-associated sleep disorder; disorders associated with difficulties in adhering to a regular sleep schedule such as sleep state misperception, shift work sleep disorder, chronic time zone change syndrome, and irregular sleep-wake syndrome; disorders associated with abnormal behaviors such as sleep terror disorder (i.e., parasomnia) and sleepwalking (i.e., somnambulism); and other disorders such as sleep bruxism, fibromyalgia, and nightmares.

The term "insomnia" refers to a sleep disorder characterized by symptoms including, without limitation, difficulty in falling asleep, difficulty in staying asleep, intermittent wakefulness, and/or waking up too early. The term also encompasses daytime symptoms such as sleepiness, anxiety, impaired concentration, impaired memory, and irritability. Types of insomnia suitable for treatment with the compositions of the present invention include, without limitation, transient, short-term, and chronic insomnia. The term "transient insomnia" refers to insomnia lasting for a few nights. The term "short-term insomnia" refers to insomnia lasting for about two to about four weeks. The term "chronic insomnia" refers to insomnia lasting for at least one month.

The phrase "prolonged awakening after sleep onset insomnia" refers to the condition wherein a subject, after falling asleep, awakens and has difficulty returning to sleep, regardless of the number of hours of time in bed remaining. "Prolonged awakening after sleep onset insomnia" includes middle-of-the-night insomnia, late night insomnia, and insomnia after early night awakening.

As used herein, the term "middle-of-the-night insomnia" or "MOTN insomnia" refers to the condition wherein a subject, after falling asleep, awakens and has difficulty returning to sleep. Typically, the subject has about 5 hours of sleep time or time in bed remaining, although in some subjects only 4 hours, 3 hours, or 2 hours of sleep time may remain. One of skill in the art will appreciate that the term middle-of-the-night refers to a middle portion of the subject's sleep time in any sleep period, rather than a specific time of a time zone, day or night. For example, a shift worker who would normally sleep from 8 am until 3 pm or 4 pm can still exhibit MOTN insomnia, when their sleep time is interrupted during normal daylight hours. MOTN insomnia can be transient, short-term, or chronic.

The term "time in bed" refers to the amount of time a subject spends in a recumbent position (e.g., lying down in bed or reclining in a chair) intending to sleep.

The term "sleep time" refers to the time that a subject spends sleeping. Sleep time can be continuous or discontinuous.

"Sleep efficiency" refers to the total sleep time a subject receives during their time in bed. Sleep efficiency is measured by the following equation:

100*(total sleep time (TST)/total time in bed).

The phrase "residual sedative effects" refers to a patient's subjective feeling of sedation upon awakening. Additionally, the term is meant to refer to a patient population as found in, for example, a clinical trial, rather than a single patient example. Residual sedative effects also can be evaluated using one or more of any of a number of tests exploring psychomotor performance, attention, information processing, and memory used by those of skill in the art including, for example, a Sleep Latency Test (SLT), a Visual Analog Test (VAT), a Digit Symbol Substitution Test (DSST), a Symbol Copying Test (SCT), a Critical Flicker Fusion threshold test (CFF), a Simple Reaction time test (visual or auditory; SRT), a Choice Reaction Time test (CRT), a Word Learning Test (WLT), a Critical Tracking Test (CTT), a Divided Attention Test (DAT), a digit or letter cancellation test, sleep staging through polysomnographic (PSG) measurements, Continuous Performance Task test (CPT), Multiple Sleep Latency Test (MSLT), a Rapid Visual Information Processing test (RVIP), a mental calculation test, a body sway test, a driving performance test, and others. Guidelines for a Sleep Latency Test are published in *Sleep* (1986) 9:519-24. The above-listed tests are described, for example, in Walsh, et al., (2000) *Clin Neuropharm* 23:17-21; Verster, et al., (2002) *J Clin Psychopharm* 22:576-583; Patat, et al, (2001) *Human Psychopharm* 16:369-392; and Hindmarch, et al., (2001) *Human Pshychopharm* 16:159-167. As a result, an amount that substantially avoids or does not produce residual sedative effects is an

amount that allows a subject, upon awakening following sleep time, to test acceptably in at least one of the above tests, preferably at least two or three of the above tests, and most preferably in at least four of the above tests.

Alternatively, an amount that substantially avoids or does not produce residual sedative effects can be objectively measured by determining the plasma or serum levels of zolpidem at an appropriate time point. In particular, residual sedative effects will be essentially extinguished when a subject's plasma levels of zolpidem fall below about 20 ng/ml. Again, this objective test refers to an average zolpidem plasma or serum concentration in a patient population. Because some variability between patients is expected, a number of patients may respond as having residual sedative effects even at low plasma or serum concentrations of zolpidem.

The term "therapeutically effective amount" or "effective amount" refers to the amount of zolpidem that is capable of achieving a therapeutic effect in a subject in need thereof. For example, an effective amount of zolpidem can be the amount that is capable of preventing or relieving one or more symptoms associated with MOTN insomnia. It is important to note that a plasma concentration time curve for any given drug is illustrative of four, very often overlapping, kinetic events that decide the fate of the drug inside the body after the drug is administered. The four events are absorption, distribution, metabolism, and excretion. The absorption phase dominates in the beginning, while the distribution phase dominates at peak concentration time, and metabolism and excretion phases dominate the remaining disappearing stages of the drug. The sedative-hypnotic activity profile of zolpidem can be predicted from its plasma concentration time curve (Greenblatt et al., *Clin. Pharmacol. Therap.* 64:553 (1998)). In general, plasma concentrations between about 25 ng/ml and about 50 ng/ml, which are sufficient for inducing sleep, occur during the absorption phase of the drug, but this is not necessarily the peak concentration. Once the zolpidem is absorbed and distributed, the plasma concentrations will fall off with time. When the latter phase of drug distribution, metabolism, and excretion results in concentrations of zolpidem below about 20 ng/ml, the residual sedative effects of the drug will be essentially extinguished. This level will depend, to some extent, on the patient's age, hepatic efficiency, and initial dose. Generally, for the compositions and methods described herein, the sedative-hypnotic activity does not persist once the plasma levels have dropped below about 20 ng/ml, due to concurrence of continuous depletion of drug in the body and fulfillment of sleep requirement of the sleep-wake cycle of the body.

The term "bioavailability" refers to the rate and/or extent to which a drug is absorbed or becomes available to the treatment site in the body. The MOTN efficacy of zolpidem can also be improved by improving the bioavailability or the absorption of zolpidem, e.g., at rate of about 0.1 ng/ml per minute.

The term "dissolves" or "dissolution" refers to the conversion of a portion of the solid dosage form to a solution or slurry form. The amount of the solid dosage form that dissolves over a period of time will vary depending on the components of the dosage form (e.g., the form of zolpidem used as well as the excipients used). Some solid dosage forms will completely dissolve in a patient's mouth over a time period of about 15 minutes or less. Still other solid dosage forms will completely dissolve in the mouth over a time period of about 6 minutes or less. Generally, at least about 25% by weight of the solid dosage form will dissolve within about 5 minutes of administration. Suitable methods known in the art for determining the dissolution profile of a solid dosage form include, e.g., United States

Pharmacopeia (USP) dissolution tests such as USP <711> Apparatus 1 or USP <711> Apparatus 2.

The term "disintegrates" or "disintegration" refers to the breakdown of, for example, a tablet or lozenge, into small pieces accompanied by complete dissolution of a substantial portion of the solid dosage form to a liquid form. More particularly, disintegration of a solid dosage form refers to less than about 25% by weight of the solid dosage form remaining in the mouth following an appropriate time period, e.g., about 5 minutes after administration. Suitable methods known in the art for determining the disintegration profile of a solid dosage form include, e.g., the USP disintegration test.

As used herein, the phrase "substantially complete conversion of zolpidem from its ionized to its un-ionized form" refers to greater than about 50% conversion of zolpidem from its ionized form into its un-ionized form. For example, a buffer system may favor at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 99% conversion of zolpidem from its ionized form into its un-ionized form. In some embodiments, the conversion occurs within about 10 minutes following administration.

The term "variability" refers to inter-subject variability in terms of the percent of relative standard deviation (RSD) for the maximum plasma concentration (C_{max}) and the time to reach the maximum plasma concentration (T_{max}). Notably, the preferred compositions of the present invention have an RSD for C_{max} of about 33% versus about 45% for commercial oral tablets such as Ambien® tablets. Further, the compositions of the present invention have an RSD for T_{max} of about 50% or less versus about 100% for commercial oral tablets such as Ambien® tablets.

The term "subject" or "patient" refers to humans.

The term "administering" refers to administration of the compositions of the present invention to the mucous membranes of the oral cavity (i.e., oral mucosa). Examples of suitable sites of administration within the oral mucosa include, without limitation, the mucous membranes of the floor of the mouth (sublingual mucosa), the cheeks (buccal mucosa), the gums (gingival mucosa), the roof of the mouth (palatal mucosa), the lining of the lips, and combinations thereof. Preferably, the compositions of the present invention are administered to the sublingual mucosa, buccal mucosa, or a combination thereof.

III. Description of the Embodiments

In one aspect, the present invention provides a solid unit dosage composition for the treatment of MOTN insomnia, the composition comprising an effective amount of zolpidem or a salt thereof, formulated for delivery of zolpidem across a subject's oral mucosa, wherein the effective amount is an amount of less than 1.30×10^{-5} moles of zolpidem, and is an amount sufficient to produce a plasma concentration between about 25 ng/ml and about 50 ng/ml within 20 minutes of administration, when evaluated in an appropriate patient population.

In one embodiment, the solid unit dosage composition provides about 50% of the maximum plasma concentration (C_{max}) of zolpidem in about 30 minutes or less, alternatively in about 20 minutes or less, or alternatively in about 10 minutes or less. In another embodiment, the solid unit dosage composition provides blood (e.g., plasma) levels of zolpidem that are less than about 20 ng/ml at a time about 2, 3, or 4 hours after dosing. The zolpidem is typically delivered across the subject's sublingual and/or buccal mucosa.

In some embodiments, the solid unit dosage composition comprises at least one pH-adjusting agent selected from the group consisting of a carbonate salt and a bicarbonate salt. In other embodiments, the solid unit dosage composition comprises a binary buffer system that raises the pH of the subject's saliva to a pH greater than about 8.5, alternatively greater than about 9.0, alternatively greater than about 9.5, alternatively greater than about 10.0, alternatively greater than about 10.5, alternatively greater than about 11.0, or alternatively between about 9.0 and about 11.0, irrespective of the starting pH of saliva. For example, the binary buffer system can comprise sodium carbonate and sodium bicarbonate. Alternatively, the binary buffer system can comprise any combination of carbonate salt and bicarbonate salt known in the art.

The solid unit dosage composition is typically in the form of a lozenge, a chewing gum, a chewable tablet, or a dissolving tablet such as a slow-dissolving tablet or a quick-dissolving tablet. Preferably, the solid unit dosage composition is a lozenge or a quick-dissolving tablet. A quick-dissolving tablet usually provides complete dissolution in the subject's mouth in less than about 0.5 minutes, alternatively in less than about 1 minute, alternatively in less than about 1.5 minutes, alternatively in less than about 2 minutes, alternatively in less than about 2.5 minutes, alternatively in less than about 3 minutes, alternatively in less than about 4 minutes, alternatively in less than about 5 minutes, or alternatively in less than about 6 minutes. A description of low dose zolpidem lozenge and tablet dosage forms is provided in Examples 1 and 3, respectively.

In another embodiment, the solid unit dosage composition contains less than about 5 mg of zolpidem hemitartrate. Preferably, the solid unit dosage composition contains from about 0.5 to about 4.75 mg of zolpidem hemitartrate, alternatively from about 1.5 to about 2.5 mg of zolpidem hemitartrate, or alternatively from about 3.0 to about 3.75 mg of zolpidem hemitartrate.

The effective amount of zolpidem is generally evaluated in an appropriate patient population (e.g., a patient population used for a clinical study) based on factors such as age, weight, the number of hours of time in bed remaining, and/or the ability of a subject to metabolize zolpidem. Accordingly, effective amounts of zolpidem for delivery across the oral mucosa may be different for selected patient populations. For example, the effective amount of zolpidem in an elderly patient population (i.e., subjects 65 years of age and older) is usually from about 1.5 mg to about 2.5 mg of zolpidem, alternatively about 1.75 mg, alternatively about 2.0 mg, or alternatively about 2.5 mg. Similarly, the effective amount of zolpidem in a population of subjects with a diminished capacity to metabolize zolpidem can be from about 1.5 mg to about 2.5 mg of zolpidem, alternatively about 1.75 mg, alternatively about 2.0 mg, or alternatively about 2.5 mg. The effective amount of zolpidem in a non-elderly patient population (i.e., subjects younger than 65 years of age) is usually from about 3.0 mg to about 3.75 mg zolpidem, alternatively about 3.25 mg, alternatively about 3.5 mg, or alternatively about 3.75 mg. The effective amount of zolpidem in subjects who have awakened but still have about 4 or 5 hours of time in bed remaining can be from about 2 mg to about 5 mg of zolpidem. A lower amount of zolpidem (e.g., from about 0.5 mg to about 2.5 mg, alternatively about 0.5 mg, alternatively about 1.0 mg, alternatively about 1.5 mg, alternatively about 2.0 mg, or alternatively about 2.5 mg) can be administered to subjects who have awakened but still have about 2 to 4 hours of time in bed remaining.

Any method known in the art can be used to determine the plasma concentration of zolpidem in a subject. As a non-limiting example, the plasma from a blood sample collected from the subject can be assayed for zolpidem levels using high pressure liquid chromatography (HPLC) followed by tandem mass spectrometry (MS) or fluorescence detection. Chromatographic methods for measuring plasma levels of zolpidem are described in, for example, Ascalone et al., *J. Chromatogr.,* 581:237-250 (1992); Tracqui et al., *J. Chromatogr.,* 616:95-103 (1993); Durol et al., *J. Anal. Toxicol.,* 215:388-392 (1997); Ptacek et al., *J. Chromatogr. B Biomed. Sci. Appl.,* 694:409-413 (1997); and Ring et al., *J. Pharm. Biomed. Anal.,* 22:495-504 (2000).

In another aspect, the present invention provides a solid unit dosage composition for the treatment of MOTN insomnia, the composition comprising an amount of zolpidem or a salt thereof effective to produce sleep within 30 minutes of dosing a subject, but does not produce residual sedative effects when the subject is awakened at a time about 4 hours after dosing, when the composition is evaluated in an appropriate patient population.

In some embodiments, the solid unit dosage composition further comprises at least one pH-adjusting agent. Examples of pH-adjusting agents include, but are not limited to, carbonate salts, bicarbonate salts, and mixtures thereof. In other embodiments, the solid unit dosage composition comprises a binary buffer system. As a non-limiting example, the binary buffer system can comprise a carbonate salt (e.g., sodium carbonate) and a bicarbonate salt (e.g., sodium bicarbonate). In a preferred embodiment, the solid unit dosage composition is in a dosage form suitable for delivery of zolpidem across the subject's oral mucosa (e.g., buccal and/or sublingual delivery), wherein the binary buffer system raises the pH of the subject's saliva to a pH greater than about 8.5, alternatively greater than about 9.0, alternatively greater than about 9.5, alternatively greater than about 10.0, alternatively greater than about 10.5, alternatively greater than about 11.0, or alternatively between about 9.0 and about 11.0, irrespective of the starting pH of saliva.

In certain embodiments, the solid unit dosage composition produces polysomnography stage 1 sleep at the onset of sleep. Polysomnography stage 1 sleep typically refers to a non-REM stage of sleep where a polysomnogram shows about a 50% reduction in activity from wakefulness. The eyes are usually closed during polysomnography stage 1 sleep, but if aroused from it, a subject may feel as if he or she has not slept. Polysomnography stage 1 sleep may last for about 5 to about 10 minutes.

In another embodiment, the solid unit dosage composition contains less than about 5 mg of zolpidem hemitartrate. Preferably, the solid unit dosage composition contains from about 0.5 to about 4.75 mg of zolpidem hemitartrate, alternatively from about 1.5 to about 2.5 mg of zolpidem hemitartrate, or alternatively from about 3.0 to about 3.75 mg of zolpidem hemitartrate.

The solid unit dosage composition is typically in the form of a lozenge, a tablet (e.g., chewable tablet, slow-dissolving tablet, quick-dissolving tablet), or a chewing gum. Preferably, the composition is a lozenge or a quick-dissolving tablet. In some embodiments, the solid unit dosage composition provides buccal and/or sublingual dissolution in about 5 minutes or less (e.g., about 4, 3, 2, 1, or 0.5 minutes or less) following administration.

In yet another aspect, the present invention provides a pharmaceutical composition suitable for absorption by the oral mucosa (e.g., buccal and/or sublingual absorption) in the treatment of MOTN insomnia, the composition comprising from about 0.5 mg to about 4.0 mg of zolpidem or a salt thereof and a pharmaceutically acceptable excipient.

In some embodiments, the pharmaceutical composition comprises from about 0.5 to about 4.0 mg of zolpidem hemitartrate. Generally, the pharmaceutical composition can comprise about 1.0 mg, alternatively about 1.75 mg, alternatively about 2.5 mg, alternatively about 3.0 mg, or alternatively about 3.5 mg, of zolpidem or a salt thereof such as zolpidem hemitartrate. In other embodiments, the pharmaceutical composition further comprises a binary buffer system. For example, the binary buffer system can comprise a carbonate such as sodium carbonate and a bicarbonate such as sodium bicarbonate. The carbonate and bicarbonate are usually present in a carbonate:bicarbonate ratio of from about 1:1.0 to about 1:1.4 by weight, or alternatively from about 1:1.0 to about 1:1.2 by weight. Preferably, the binary buffer system raises the pH of the subject's saliva to a pH greater than about 8.5, alternatively greater than about 9.0, alternatively greater than about 9.5, alternatively greater than about 10.0, alternatively greater than about 10.5, alternatively greater than about 11.0, or alternatively between about 9.0 and about 11.0, irrespective of the starting pH of saliva.

In certain embodiments, the pharmaceutical composition is a solid unit dosage form such as a lozenge or tablet (e.g., chewable tablet, slow-dissolving tablet, quick-dissolving tablet). In another embodiment, the pharmaceutical composition provides complete buccal and/or sublingual dissolution in about 5 minutes or less (e.g., about 4, 3, 2, 1, or 0.5 minutes or less) following administration.

In a further aspect, the present invention provides a solid pharmaceutical composition for delivery across the oral mucosa for treating insomnia comprising zolpidem in an amount less than 5 mg and a buffer.

Generally, the buffer comprises a carbonate buffer, a bicarbonate buffer, or a mixture thereof. In certain instances, the buffer is a binary buffer comprising, e.g., a carbonate buffer and a bicarbonate buffer.

In some embodiments, the amount of zolpidem is less than about 1.30×10^{-5} moles of zolpidem. In other embodiments, the amount of zolpidem is from about 0.5 to about 4.75 mg of zolpidem hemitartrate, e.g., from about 1.5 to about 2.5 mg of zolpidem hemitartrate, alternatively from about 3.0 to about 3.75 mg of zolpidem hemitartrate, alternatively from about 1.0 to about 3.75 mg of zolpidem hemitartrate, or alternatively from about 1.5 to about 3.0 mg of zolpidem hemitartrate.

The solid pharmaceutical composition is typically in a dosage form including, but not limited to, a lozenge, a chewing gum, a chewable tablet, and a dissolving tablet such as a slow-dissolving tablet or a quick-dissolving tablet. Preferably, the solid pharmaceutical composition is in the form of a lozenge or a quick-dissolving sublingual tablet. The zolpidem is typically delivered across the sublingual and/or buccal mucosa.

In a related aspect, the present invention provides a solid pharmaceutical composition for delivery across the oral mucosa for treating insomnia comprising zolpidem in an amount less than about 5 mg and a binary buffer.

In one embodiment, the amount of zolpidem is from about 0.5 to about 4.75 mg of zolpidem hemitartrate. Preferably, the amount of zolpidem is from about 1.5 to about 2.5 mg of zolpidem hemitartrate, alternatively from about 3.0 to about 3.75 mg of zolpidem hemitartrate, alternatively from about 1.0 to about 3.75 mg of zolpidem hemitartrate, or alternatively from about 1.5 to about 3.0 mg of zolpidem hemitartrate. In certain other instances, the amount of zolpidem is less than about 1.30×10^{-5} moles of zolpidem.

In some embodiments, the binary buffer comprises a carbonate buffer such as sodium carbonate and a bicarbonate buffer such as sodium bicarbonate. Preferably, the solid pharmaceutical composition is a lozenge or tablet such as a sublingual tablet.

In another related aspect, the present invention provides a solid unit dosage pharmaceutical composition comprising a dose of zolpidem hemitartrate in an amount of less than about 5 mg and a binary buffer system capable of raising the pH of a subject's saliva to a pH greater than about 8.5, alternatively greater than about 9.0, alternatively greater than about 9.5, alternatively greater than about 10.0, alternatively greater than about 10.5, alternatively greater than about 11.0, or alternatively between about 9.0 and about 11.0, irrespective of the starting pH of saliva, wherein the composition is formulated for delivery of zolpidem across the subject's oral mucosa.

In one embodiment, the solid unit dosage pharmaceutical composition contains from about 0.5 to about 4.75 mg of zolpidem hemitartrate. Preferably, the solid unit dosage pharmaceutical composition contains from about 1.5 to about 2.5 mg of zolpidem hemitartrate, alternatively from about 3.0 to about 3.75 mg of zolpidem hemitartrate, alternatively from about 1.0 to about 3.75 mg of zolpidem hemitartrate, or alternatively from about 1.5 to about 3.0 mg of zolpidem hemitartrate.

In some embodiments, the binary buffer system comprises a carbonate salt such as sodium carbonate and a bicarbonate salt such as sodium bicarbonate. In other embodiments, the binary buffer system comprises a carbonate salt and a bicarbonate salt in a carbonate:bicarbonate ratio of from about 1:1.0 to about 1:1.4 by weight, or alternatively from about 1:1.0 to about 1:1.2 by weight.

In an additional aspect, the present invention provides a pharmaceutical composition for treating insomnia comprising zolpidem in an amount less than 5 mg and a binary buffer.

The pharmaceutical composition is typically in a dosage form suitable for delivery of zolpidem across a subject's oral mucosa (e.g., buccal and/or sublingual delivery) including, but not limited to, a lozenge, a chewing gum, a chewable tablet, and a dissolving tablet such as a slow-dissolving tablet or a quick-dissolving tablet. In some embodiments, the binary buffer comprises a carbonate buffer such as sodium carbonate and a bicarbonate buffer such as sodium bicarbonate. Alternatively, the binary buffer can comprise any combination of carbonate salt and bicarbonate salt known in the art.

In a related aspect, the present invention provides a pharmaceutical composition for treating insomnia comprising zolpidem in an amount less than 5 mg and a binary buffer, wherein the composition is formulated for delivery of zolpidem across the oral mucosa (e.g., buccal and/or sublingual mucosa) and the binary buffer produces a saliva pH of at least about 8.5, alternatively at least about 9.0, alternatively at least about 9.5, alternatively at least about 10.0, alternatively at least about 10.5, alternatively at least about 11.0, or alternatively between about 9.0 and about 11.0, irrespective of the starting saliva pH.

In another aspect, the present invention provides a method of treating insomnia, the method comprising:

administering to a subject who awakens from sleep and desires to return to sleep within 30 minutes and sleep for less than 5 hours, a single unit dosage composition comprising an effective amount of zolpidem or a salt thereof, formulated for delivery of zolpidem across the subject's oral mucosa,

wherein the effective amount is an amount of less than 1.30×10^{-5} moles of zolpidem, and is an amount sufficient to produce a plasma concentration between about 25 ng/ml and

about 50 ng/ml within 20 minutes of administration, when evaluated in an appropriate patient population.

In the methods of the present invention, the single unit dosage composition is typically administered pro re nata ("as needed"). Preferably, the single unit dosage composition is a lozenge or tablet (e.g., chewable tablet, slow-dissolving tablet, quick-dissolving tablet) formulated for buccal and/or sublingual delivery of zolpidem. In some embodiments, the single unit dosage composition further comprises a binary buffer system that raises the pH of the subject's saliva to a pH greater than about 8.5, alternatively greater than about 9.0, alternatively greater than about 9.5, alternatively greater than about 10.0, alternatively greater than about 10.5, alternatively greater than about 11.0, or alternatively between about 9.0 and about 11.0, irrespective of the starting pH of saliva.

In a preferred embodiment, the single unit dosage composition comprises from about 0.5 to about 4.75 mg of zolpidem hemitartrate and a binary buffer system that raises the pH of the subject's saliva to a pH greater than about 8.5, alternatively greater than about 9.0, alternatively greater than about 9.5, alternatively greater than about 10.0, alternatively greater than about 10.5, alternatively greater than about 11.0, or alternatively between about 9.0 and about 11.0, irrespective of the starting pH of saliva. In one embodiment, the binary buffer system comprises sodium carbonate and sodium bicarbonate.

In a related aspect, the present invention provides a method of treating MOTN insomnia in a subject, the method comprising:

administering to the subject a pharmaceutical composition comprising zolpidem or a salt thereof in an amount of less than 1.30×10^{-5} moles of zolpidem,

wherein the administering is on an as-needed basis, and wherein delivery of zolpidem occurs across the subject's oral mucosa to produce a blood level of zolpidem in the subject between about 25 ng/ml and about 50 ng/ml within about 20 minutes of administration and less than 20 ng/ml at a time 4 hours after administration.

In one embodiment, the pharmaceutical composition provides blood (e.g., plasma) levels of zolpidem in the subject between about 25 ng/ml and about 50 ng/ml within about 20, 30, or 40 minutes of administration and less than about 20 ng/ml at a time about 2, 3, or 4 hours after administration. In another embodiment, the pharmaceutical composition provides about 50% of the maximum plasma concentration (C_{max}) of zolpidem in about 30 minutes or less, alternatively in about 20 minutes or less, or alternatively in about 10 minutes or less, following administration. Methods for determining the blood (e.g., plasma) level of zolpidem in a subject are described above. The delivery of zolpidem typically occurs across the subject's sublingual and/or buccal mucosa.

In some embodiments, the pharmaceutical composition comprises at least one pH-adjusting agent. Examples of pH-adjusting agents include, but are not limited to, carbonate salts, bicarbonate salts, and mixtures thereof. In other embodiments, the pharmaceutical composition comprises a binary buffer system that raises the pH of the subject's saliva to a pH greater than about 8.5, alternatively greater than about 9.0, alternatively greater than about 9.5, alternatively greater than about 10.0, alternatively greater than about 10.5, alternatively greater than about 11.0, or alternatively between about 9.0 and about 11.0, irrespective of the starting pH of saliva. For example, the binary buffer system can comprise sodium carbonate and sodium bicarbonate. Alternatively, the binary buffer system can comprise any combination of carbonate salt and bicarbonate salt known in the art.

The pharmaceutical composition is typically in the form of a lozenge, a chewing gum, a chewable tablet, or a dissolving tablet such as a slow-dissolving tablet or a quick-dissolving tablet (e.g., quick-dissolving sublingual tablet). In another embodiment, the pharmaceutical composition contains less than about 5 mg of zolpidem hemitartrate. An effective amount of zolpidem to be administered on an as-needed basis according to the methods of the present invention is described above. Preferably, the pharmaceutical composition contains from about 0.5 to about 4.75 mg of zolpidem hemitartrate, alternatively from about 1.5 to about 2.5 mg of zolpidem hemitartrate, or alternatively from about 3.0 to about 3.75 mg of zolpidem hemitartrate. In certain instances, the pharmaceutical composition comprises less than a 5 mg dose of zolpidem hemitartrate and a binary buffer system consisting of a carbonate salt and a bicarbonate salt.

In yet another aspect, the present invention provides a method of treating insomnia in a subject, the method comprising:

administering to the subject a pharmaceutical composition comprising zolpidem or a salt thereof,

wherein the composition provides delivery of zolpidem across the subject's oral mucosa, wherein the subject is a subject who awakens from sleep and desires to resume sleep for less than 5 hours, and wherein the composition produces sleep within 30 minutes of dosing and the dose is such that it does not produce residual sedative effects when the subject is awakened at a time 4 hours after dosing.

In one embodiment, the pharmaceutical composition produces sleep within about 20, 30, or 40 minutes of dosing but does not produce residual sedative effects when the subject is awakened at a time about 2, 3, or 4 hours after dosing. In certain instances, the pharmaceutical composition produces polysomnography stage 1 sleep at the onset of sleep.

In another embodiment, the pharmaceutical composition produces blood (e.g., plasma) levels of zolpidem in the subject between about 25 ng/ml and about 50 ng/ml within about 20, 30, or 40 minutes of administration and/or less than about 20 ng/ml at a time about 2, 3, or 4 hours after administration. In yet another embodiment, the pharmaceutical composition provides about 50% of the maximum plasma concentration (C_{max}) of zolpidem in about 30 minutes or less, alternatively in about 20 minutes or less, or alternatively in about 10 minutes or less, following administration. The zolpidem is typically delivered across the subject's sublingual and/or buccal mucosa.

In some embodiments, the pharmaceutical composition further comprises at least one pH-adjusting agent. In other embodiments, the pharmaceutical composition further comprises a binary buffer system that raises the pH of the subject's saliva to a pH greater than about 8.5, alternatively greater than about 9.0, alternatively greater than about 9.5, alternatively greater than about 10.0, alternatively greater than about 10.5, alternatively greater than about 11.0, or alternatively between about 9.0 and about 11.0, irrespective of the starting pH of saliva. Preferably, the pharmaceutical composition comprises zolpidem hemitartrate, e.g., in an amount of less than about 5 mg. In certain instances, the pharmaceutical composition comprises from about 0.5 to about 4.75 mg of zolpidem hemitartrate, e.g., from about 1.5 to about 2.5 mg of zolpidem hemitartrate, alternatively from about 3.0 to about 3.75 mg of zolpidem hemitartrate, alternatively from about 1.0 to about 3.75 mg of zolpidem hemitartrate, or alternatively from about 1.5 to about 3.0 mg of zolpidem hemitartrate.

In a preferred embodiment, the pharmaceutical composition comprises from about 1.5 to about 2.5 mg of zolpidem hemitartrate or from about 3.0 to about 3.75 mg of zolpidem

hemitartrate and a binary buffer system consisting of sodium carbonate and sodium bicarbonate.

The pharmaceutical composition is typically in a solid unit dosage form including, but not limited to, a lozenge, a chewing gum, a chewable tablet, and a dissolving tablet such as a slow-dissolving tablet or a quick-dissolving tablet. Preferably, the pharmaceutical composition is in the form of a lozenge or a quick-dissolving sublingual tablet.

In a further aspect, the present invention provides a method of treating insomnia in a subject, the method comprising:

administering a solid pharmaceutical composition comprising zolpidem in an amount less than 5 mg and a buffer, to a subject who awakens from sleep and desires to resume sleep for less than 5 hours,

wherein the solid pharmaceutical composition provides delivery of zolpidem across the subject's oral mucosa, and wherein a blood level of zolpidem is achieved in the subject of between about 25 ng/ml and about 50 ng/ml within about 20 minutes of administration.

In a related aspect, the present invention provides a method of treating insomnia, the method comprising the steps of:

providing a solid pharmaceutical composition comprising zolpidem in an amount less than 5 mg and a buffer to a patient who awakens from sleep and desires to resume sleep for less than 5 hours; and

administering the solid pharmaceutical composition to the patient for delivery of the zolpidem across the patient's oral mucosa,

wherein a blood level of zolpidem in the patient is between about 25 ng/ml and about 50 ng/ml within about 20 minutes of administration.

In one embodiment, the solid pharmaceutical composition achieves a blood (e.g., plasma) level of zolpidem in the subject between about 25 ng/ml and about 50 ng/ml within about 20, 30, or 40 minutes of administration. In another embodiment, the solid pharmaceutical composition provides a blood level of zolpidem in the subject less than about 20 ng/ml within about 2, 3, or 4 hours of administration.

In some embodiments, the solid pharmaceutical composition dissolves or disintegrates in the subject's mouth in about 2 minutes or less (e.g., about 2, 1.5, 1, or 0.5 minutes or less). In other embodiments, the solid pharmaceutical composition dissolves or disintegrates in the subject's mouth in about 3 to about 6 minutes (e.g., about 3, 3.5, 4, 4.5, 5, 5.5, or 6 minutes). The zolpidem is typically delivered across the subject's sublingual and/or buccal mucosa.

Generally, the buffer that is present in the pharmaceutical composition raises the pH of saliva in the subject's mouth to a pH greater than about 8.5, alternatively greater than about 9.0, alternatively greater than about 9.5, alternatively greater than about 10.0, alternatively greater than about 10.5, alternatively greater than about 11.0, or alternatively between about 9.0 and about 11.0, irrespective of the starting pH of saliva. Preferably, the pH of the saliva is raised above about 9.0 for at least about 2 minutes (e.g., about 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, or more minutes). In certain instances, the buffer is a binary buffer. A non-limiting example of a suitable binary buffer includes a mixture of a carbonate buffer and a bicarbonate buffer.

In an additional aspect, the present invention provides a method of treating insomnia, the method comprising:

administering a solid pharmaceutical composition comprising zolpidem in an amount less than 5 mg and a binary buffer, to a subject who awakens from sleep and desires to resume sleep for less than 5 hours,

wherein the solid pharmaceutical composition provides delivery of zolpidem across the subject's oral mucosa, wherein the solid pharmaceutical composition dissolves or disintegrates in about 2 minutes or less in the subject's mouth, and wherein the binary buffer raises the pH of saliva in the subject's mouth to a pH greater than about 9.0.

In a related aspect, the present invention provides a method of treating insomnia, the method comprising the steps of:

providing a solid pharmaceutical composition comprising zolpidem in an amount less than 5 mg and a binary buffer to a patient who awakens from sleep and desires to resume sleep for less than 5 hours; and

administering the solid pharmaceutical composition to the patient for delivery of the zolpidem across the patient's oral mucosa,

wherein the solid pharmaceutical composition dissolves or disintegrates in about 2 minutes or less in the patient's mouth, and wherein the binary buffer raises the pH of saliva in the patient's mouth to a pH greater than about 9.0.

In one embodiment, the solid pharmaceutical composition achieves a blood (e.g., plasma) level of zolpidem in the subject between about 25 ng/ml and about 50 ng/ml within about 20, 30, or 40 minutes of administration. In another embodiment, the solid pharmaceutical composition provides a blood level of zolpidem in the subject less than about 20 ng/ml within about 2, 3, or 4 hours of administration.

In some embodiments, the pH of the saliva is raised above about 9.0 for at least about 2 minutes (e.g., 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, or more minutes). In other embodiments, the binary buffer comprises a carbonate buffer and a bicarbonate buffer. The zolpidem is typically delivered across the subject's sublingual and/or buccal mucosa.

IV. Compositions

Typically, the compositions of the present invention will contain zolpidem or a salt thereof in an amount of about 0.5 mg, about 0.8 mg, about 1.0 mg, about 1.5 mg, about 1.75 mg, about 2.0 mg, about 2.5 mg, about 3.0 mg, about 3.5 mg, about 3.75 mg, about 4.0 mg, about 4.5 mg, or about 4.75 mg per administration. However, the amount of zolpidem can be any dose amount less than about 5 mg, alternatively from about 1.5 to about 2.5 mg, or alternatively from about 3.0 to about 3.75 mg. One skilled in the art will appreciate that the amount of zolpidem can be expressed as the number of moles of zolpidem present in the composition. For example, 5 mg of zolpidem hemitartrate is equivalent to about 1.30×10^{-5} moles of zolpidem. As such, in some embodiments, the composition will contain an amount of zolpidem hemitartrate that provides less than about 1.30×10^{-5} moles of zolpidem.

Any form of zolpidem is suitable for use in the compositions described herein, e.g., a salt form of zolpidem, a free base form of zolpidem, a polymorph of zolpidem, or a mixture thereof. For example, pharmaceutically acceptable salts of zolpidem can include, without limitation, tartrate, hemitartrate, succinate, dihydrochloride, salicylate, hemisuccinate, citrate, maleate, hydrochloride, carbamate, sulfate, nitrate, and benzoate salt forms, as well as combinations thereof. In some embodiments, the zolpidem is in the form of a salt, e.g., zolpidem hemitartrate. In other embodiments, the zolpidem is in the form of a polymorph, e.g., commercially available from Plantex Ltd. (Netanya, Israel).

The compositions of the present invention may take the form of solid, semi-solid, lyophilized powder, or liquid dosage forms, such as, for example, tablets (e.g., chewable, slow-dissolving, quick-dissolving, etc.), pills, capsules, lozenges, gums, powders, solutions, suspensions, emulsions, aerosols, foams, creams, gels, lotions, or the like. Preferably, the compositions of the present invention are formulated as a tablet or

a lozenge, in particular quick-dissolving tablets or lozenges, such as those described in U.S. Patent Publication No. 20050226925.

As used herein, the term "unit dosage" or "dosage form" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of therapeutic agent calculated to produce the desired onset, tolerability, and therapeutic effects, in association with one or more suitable pharmaceutical excipients such as carriers. Methods for preparing such dosage forms are known or will be apparent to those skilled in the art. For example, in some embodiments, a chewing gum dosage form of the present invention can be prepared according to the procedures set forth in U.S. Pat. No. 4,405,647. In other embodiments, a liquid spray or a solution, tincture, tablet, lozenge, or candy dosage form of the present invention can be prepared according to the procedures set forth, for example, in *Remington: The Science and Practice of Pharmacy,* 20th Ed., Lippincott, Williams & Wilkins (2003); *Pharmaceutical Dosage Forms, Volume* 1*: Tablets,* 2nd Ed., Marcel Dekker, Inc., New York, N.Y. (1989); and similar publications. The dosage form to be administered will, in any event, contain a quantity of the therapeutic agent in a therapeutically effective amount for relief of the condition being treated when administered in accordance with the teachings of the present invention.

The terms "carrier" or "excipient" refer to a typically inert substance used as a diluent or vehicle for a drug such as a therapeutic agent. The term also encompasses a typically inert substance that imparts cohesive qualities to the composition. Suitable carriers for use in the compositions of the present invention include, without limitation, a binder, a gum base, and combinations thereof. Non-limiting examples of binders include mannitol, sorbitol, xylitol, maltodextrin, lactose, dextrose, sucrose, glucose, inositol, powdered sugar, molasses, starch, cellulose, microcrystalline cellulose, polyvinylpyrrolidone, acacia gum, guar gum, tragacanth gum, alginate, extract of Irish moss, panwar gum, ghatti gum, mucilage of isapol husks, Veegum®, larch arabogalactan, gelatin, methylcellulose, ethylcellulose, carboxymethylcellulose, hydroxypropylmethylcellulose, polyoxyethylene polymers, polyacrylic acid (e.g., Carbopol), calcium silicate, calcium phosphate, dicalcium phosphate, calcium sulfate, kaolin, sodium chloride, polyethylene glycol, propylene glycol, and combinations thereof. These binders can be pre-processed to improve their flowability and taste by methods known in the art such as freeze drying (see, e.g., Fundamentals of Freeze-Drying, *Pharm. Biotechnol.,* 14:281-360 (2002); Lyophililization of Unit Dose Pharmaceutical Dosage Forms, *Drug. Dev. Ind. Pharm.,* 29:595-602 (2003)); solid-solution preparation (see, e.g., U.S. Pat. No. 6,264,987); and lubricant dusting and wet-granulation preparation with a suitable lubricating agent (see, e.g., *Remington: The Science and Practice of Pharmacy*, supra). For example, Mannogem® and Sorbogem®, sold by SPI Pharma Group (New Castle, Del.), are freeze-dried processed forms of mannitol and sorbitol, respectively. Typically, the compositions of the present invention comprise from about 25% to about 90% by weight of the binder, and preferably from about 50% to about 80%. However, one skilled in the art will appreciate that the compositions of the present invention can be made without any binders, e.g., to produce a highly friable dosage form.

Non-limiting examples of gum bases include materials selected from among the many water-insoluble and saliva-insoluble gum base materials known in the art. For example, in some instances, the gum base comprises at least one hydrophobic polymer and at least one hydrophilic polymer. Non-limiting examples of suitable hydrophobic and hydrophilic polymers for gum bases include both natural and synthetic polymers such as elastomers, rubbers, and combinations thereof. Examples of suitable natural polymers include, without limitation, substances of plant origin such as chicle, jelutong, gutta percha, crown gum, and combinations thereof. Examples of suitable synthetic polymers include elastomers such as butadiene-styrene copolymers, isobutylene and isoprene copolymers (e.g., "butyl rubber"), polyethylene, polyisobutylene, polyvinylester (e.g., polyvinyl acetate and polyvinyl acetate phthalate), and combinations thereof. In other instances, the gum base comprises a mixture of butyl rubber (i.e., isobutylene and isoprene copolymer), polyisobutylene, and optionally, polyvinylacetate (e.g., having a molecular weight of approximately 12,000). Typically, the gum base comprises from about 25% to about 75% by weight of these polymers, and preferably from about 30% to about 60%.

The compositions of the present invention can additionally include lubricating agents; wetting agents; emulsifying agents; solubilizing agents; suspending agents; preserving agents such as methyl-, ethyl-, and propyl-hydroxy-benzoates, butylated hydroxytoluene, and butylated hydroxyanisole; sweetening agents; flavoring agents; coloring agents; and disintegrating agents such as crospovidone as well as croscarmellose sodium and other cross-linked cellulose polymers.

Lubricating agents can be used to prevent adhesion of the dosage form to the surface of the dies and punches, and to reduce inter-particle friction. Lubricating agents may also facilitate ejection of the dosage form from the die cavity and improve the rate of granulation flow during processing. Examples of suitable lubricating agents include, without limitation, magnesium stearate, calcium stearate, zinc stearate, stearic acid, sodium stearyl fumarate, simethicone, silicon dioxide, talc, hydrogenated vegetable oil, polyethylene glycol, mineral oil, and combinations thereof. The compositions of the present invention can comprise from about 0% to about 10% by weight of the lubricating agent, and preferably from about 1% to about 5%.

Sweetening agents can be used to improve the palatability of the composition by masking any unpleasant tastes it may have. Examples of suitable sweetening agents include, without limitation, compounds selected from the saccharide family such as the mono-, di-, tri-, poly-, and oligosaccharides; sugars such as sucrose, glucose (corn syrup), dextrose, invert sugar, fructose, maltodextrin, and polydextrose; saccharin and salts thereof such as sodium and calcium salts; cyclamic acid and salts thereof; dipeptide sweeteners; chlorinated sugar derivatives such as sucralose and dihydrochalcone; sugar alcohols such as sorbitol, sorbitol syrup, mannitol, xylitol, hexa-resorcinol, and the like, and combinations thereof. Hydrogenated starch hydrolysate, and the potassium, calcium, and sodium salts of 3,6-dihydro-6-methyl-1-1,2,3-oxathiazin-4-one-2,2-dioxide may also be used. Of the foregoing, sorbitol, mannitol, and xylitol, either alone or in combination, are preferred sweetening agents. The compositions of the present invention can comprise from about 0% to about 80% by weight of the sweetening agent, preferably from about 5% to about 75%, and more preferably from about 25% to about 50%.

Flavoring agents can also be used to improve the palatability of the composition. Examples of suitable flavoring agents include, without limitation, natural and/or synthetic (i.e., artificial) compounds such as peppermint, spearmint, wintergreen, cinnamon, menthol, cherry, strawberry, watermelon, grape, banana, peach, pineapple, apricot, pear, raspberry, lemon, grapefruit, orange, plum, apple, fruit punch, passion

fruit, chocolate (e.g., white, milk, dark), vanilla, caramel, coffee, hazelnut, combinations thereof, and the like. Coloring agents can be used to color code the composition, for example, to indicate the type and dosage of the therapeutic agent therein. Suitable coloring agents include, without limitation, natural and/or artificial compounds such as FD & C coloring agents, natural juice concentrates, pigments such as titanium oxide, silicon dioxide, and zinc oxide, combinations thereof, and the like. The compositions of the present invention can comprise from about 0% to about 10% by weight of the flavoring and/or coloring agent, preferably from about 0.1% to about 5%, and more preferably from about 2% to about 3%.

When the dosage form is a chewing gum, the composition can comprise zolpidem or a pharmaceutically acceptable salt thereof ("therapeutic agent"), a carrier or excipient such as a gum base, a pH-adjusting agent or buffer system, and optionally a protecting agent. The chewing gum composition may further comprise lubricating agents, wetting agents, emulsifying agents, solubilizing agents; suspending agents, preserving agents, sweetening agents, flavoring agents, and coloring agents. Typically, the chewing gum composition comprises less than about 5 mg (e.g., from about 0.5 mg to about 4.75 mg, from about 1.5 mg to about 2.5 mg, from about 3.0 mg to about 3.75 mg, etc.) of zolpidem or a salt thereof. One skilled in the art understands that the foregoing amounts will vary depending upon the particular source of zolpidem utilized, the amount of zolpidem desired in the final formulation, as well as on the particular release rate of zolpidem desired. In certain instances, the buffer system of the chewing gum composition provides a final salivary pH in excess of at least about 7.8, preferably at least about 8.5, and more preferably at least about 9 (e.g., about 9-11). The chewing gum composition typically comprises from about 20% to about 95% by weight of the gum base, more typically from about 30% to about 85%, and most typically from about 50% to about 70% of the gum base.

The chewing gum composition may further comprise a protecting agent. The protecting agent coats at least part of the therapeutic agent, typically upon the mixing of the two agents. The protecting agent may be mixed with the therapeutic agent in a ratio of from about 0.1 to about 100 by weight, preferably in a ratio of from about 1 to about 50, and more preferably in a ratio of from about 1 to about 10. Without being bound to any particular theory, the protecting agent reduces the adhesion between the therapeutic agent and the gum base so that the therapeutic agent may be more easily released from the gum base. In this way, the therapeutic agent may be delivered across the mucous membranes of the oral cavity within about 5 to about 20 minutes of chewing, preferably within about 10 minutes of chewing. A variety of different protecting agents may be used. Examples of suitable protecting agents include, without limitation, calcium stearate, glycerin monostearate, glyceryl behenate, glyceryl palmitostearate, hydrogenated castor oil, hydrogenated vegetable oil type I, light mineral oil, magnesium lauryl sulfate, magnesium stearate, sodium stearyl fumarate, mineral oil, poloxamer, polyethylene gycol, sodium benzoate, sodium chloride, sodium lauryl sulfate, stearic acid, cab-o-sil, talc, zinc stearate, and combinations thereof.

The gum base may additionally include plasticizers such as softeners or emulsifiers. Such plasticizers may, for example, help reduce the viscosity of the gum base to a desirable consistency and improve its overall texture and bite. Plasticizers may also facilitate the release of the therapeutic agent upon mastication. Non-limiting examples of plasticizers include lecithin, mono- and diglycerides, lanolin, stearic acid, sodium stearate, potassium stearate, glycerol triacetate, glycerol monostearate, glycerin, and combinations thereof. The gum base typically comprises from about 0% to about 20% by weight of the plasticizer, and more typically from about 5% to about 15%.

The gum base may further comprise waxes such as beeswax and microcrystalline wax, fats or oils such as soybean and cottonseed oil, and combinations thereof. Typically, the gum base comprises from about 0% to about 25% by weight of these waxes and oils, and more typically comprises from about 15% to about 20%.

In addition, the gum base may further comprise one or more elastomeric solvents such as rosins and resins. Non-limiting examples of such solvents include methyl, glycerol, and pentaerythritol esters of rosins, modified rosins such as hydrogenated, dimerized or polymerized rosins, or combinations thereof (e.g., pentaerythritol ester of partially hydrogenated wood rosin, pentaerythritol ester of wood rosin, glycerol ester of wood rosin, glycerol ester of partially dimerized rosin, glycerol ester of polymerized rosin, glycerol ester of tall oil rosin, glycerol ester of wood rosin and partially hydrogenated wood rosin and partially hydrogenated methyl ester of rosin such as polymers of alpha-pinene or beta-pinene, terpene resins including polyterpene, and combinations thereof). Typically, the gum base comprises from about 0% to about 75% by weight of the elastomeric solvent, and more typically less than about 10%.

The gum base may further comprise a filler material to enhance the chewability of the final chewing gum composition. Fillers that are substantially non-reactive with other components of the final chewing gum formulation are preferable. Examples of suitable fillers include, without limitation, calcium carbonate, magnesium silicate (i.e., talc), dicalcium phosphate, metallic mineral salts (e.g., alumina, aluminum hydroxide, and aluminum silicates), and combinations thereof. Typically, the gum base comprises from about 0% to about 30% by weight of the filler, and more typically from about 10% to about 20%.

One skilled in the art will appreciate that the gum base need not be prepared from its individual components. For example, the gum base can be purchased with the desired ingredients contained therein, and can be modified to include additional agents. Several manufacturers produce gum bases suitable for use with the described chewing gum compositions. Examples of such gum bases include, without limitation, Pharmagum™ M, S, or C(SPI Pharma Group; New Castle, Del.). In general, Pharmagum™ comprises a mixture of gum base, sweetening agent, plasticizer, and sugar.

In certain instances, the chewing gum composition includes a therapeutic agent centerfill. A centerfill may be particularly suitable when immediate release of the therapeutic agent is preferred. In addition, encapsulating the therapeutic agent in a centerfill may help to mask any undesirable taste that the therapeutic agent may have. In these instances, the gum base surrounds, at least in part, a centerfill. The centerfill comprises at least one therapeutic agent, and may be a liquid or semi-liquid material. The centerfill material can be a synthetic polymer, a semi-synthetic polymer, low-fat, or fat-free and contain one or more sweetening agents, flavoring agents, coloring agents, and/or scenting agents. Preferably, the centerfill includes a buffer system as described herein. Methods for preparing a centerfill chewing gum are described, for example, in U.S. Pat. No. 3,806,290.

The chewing gum compositions can have any desired shape, size, and texture. For example, the chewing gum can have the shape of a stick, tab, gumball, and the like. Similarly, the chewing gum can be any desirable color. For example, the

chewing gum can be any shade of red, blue, green, orange, yellow, violet, indigo, and mixtures thereof, and can be color coded to indicate the type and dosage of the therapeutic agent therein. The chewing gum can be individually wrapped or grouped together in pieces for packaging by methods well known in the art.

When the dosage form is a tablet such as a dissolving tablet or chewable tablet, the composition can comprise zolpidem or a pharmaceutically acceptable salt thereof, a carrier or excipient such as a binder, and a pH-adjusting agent or buffer system. The tablet composition may further comprise protecting agents, lubricating agents, wetting agents, emulsifying agents, solubilizing agents; suspending agents, preserving agents, sweetening agents, flavoring agents, coloring agents, and disintegrating agents. Typically, the tablet compositions of the present invention comprise less than about 5 mg (e.g., from about 0.5 mg to about 4.75 mg, from about 1.5 mg to about 2.5 mg, from about 3.0 mg to about 3.75 mg, etc.) of zolpidem or a salt thereof. One skilled in the art understands that the foregoing amounts will vary depending upon the particular source of zolpidem utilized, the amount of zolpidem desired in the final formulation, as well as on the particular release rate of zolpidem desired. In certain instances, the buffer system of the tablet compositions provide a final salivary pH in excess of at least about 7.8, preferably at least about 8.5, and more preferably at least about 9 (e.g., about 9-11).

In certain embodiments, the tablet is a dissolving tablet such as a slow-dissolving or quick-dissolving tablet that is dissolved by a subject's saliva, without the need for chewing. For example, a dissolving tablet placed on the subject's tongue can be used for buccal delivery of the therapeutic agent. Alternatively, a dissolving tablet placed underneath the subject's tongue can be used for sublingual delivery of the therapeutic agent. This type of dosage form may be particularly desirable for pediatric and geriatric patients, since small children and aged individuals often have difficulty chewing certain items. Typically, the dissolving tablet is formulated to dissolve within about 1 to about 15 minutes, preferably within about 2 to about 10 minutes, e.g., within about 2, 3, 4, 5, 6, 7, 8, 9, or 10 minutes, following administration. One skilled in the art will understand that quick-dissolving tablets dissolve faster than slow-dissolving tablets, which are typically dissolved gradually rather than rapidly by a subject's saliva. In a preferred embodiment, the slow-dissolving or quick-dissolving tablet delivers the therapeutic agent across the sublingual mucosa.

In certain other embodiments, the tablet is a chewable tablet that is chewed by a subject and formulated to dissolve either rapidly or gradually. For example, a chewable tablet placed on the subject's tongue can be used for buccal delivery of the therapeutic agent. During chewing, the chewable tablet can be moved around within the mouth and can sometimes be parked between the gums and the cheeks or underneath the tongue. As a result, at least a portion of the therapeutic agent contained within a chewable tablet may also be delivered sublingually (i.e., across the sublingual mucosa). Typically, the chewable tablet is formulated to dissolve within about 1 to about 15 minutes, preferably within about 2 to about 10 minutes, e.g., within about 2, 3, 4, 5, 6, 7, 8, 9, or 10 minutes, following administration.

As described above, the dissolving and chewable tablets of the present invention are typically formulated to dissolve within about 1 to about 15 minutes following administration. However, while these time frames are amenable to maximum exposure of the therapeutic agent to the oral mucosa (e.g., to the sublingual and/or buccal mucosa), they are not always amenable to user compliance (e.g., users may swallow too frequently and, therefore, hinder maximal transmucosal absorption). Consequently, in certain instances, it may be desirable to strike a balance between patient compliance and maximum exposure time of the therapeutic agent to the oral mucosa. This can be accomplished, for example, by reducing the tablet size (e.g., from about 700-800 mg to about 200-300 mg or about 100-350 mg) without reducing the concentration or amount per unit dose of the buffer system or the therapeutic agent. In addition, subtle changes to the tablet formulation such as, for example, replacing one flavoring agent for another (e.g., chocolate for spearmint) or replacing one binder or sweetening agent for another (e.g., lactose for mannitol or sorbitol) may be used to reduce salivation.

The carrier or excipient present in the tablets of the present invention is typically a binder that is useful in keeping the tablet in a semi-solid state, and may be a solid or a liquid, and may for example be a high-melting point fat or waxy material. Materials suitable as binders are discussed in detail above and may be used alone or in combination in the tablet compositions of the present invention. In addition, binders such as mannitol, sorbitol, lactose, sucrose, and inositol can impart properties to the tablet that permit or enhance its disintegration in the mouth.

The tablet composition may also comprise one or more elastomeric solvents such as rosins and resins. Non-limiting examples of such solvents are discussed in detail above and may be used alone or in combination in the tablet compositions of the present invention. In addition, the tablet composition may further comprise waxes such as beeswax and microcrystalline wax, fats or oils such as soybean and cottonseed oil, and combinations thereof. Moreover, the tablet composition may additionally include plasticizers such as softeners or emulsifiers. Such plasticizers may, for example, help reduce the viscosity of the salivary solution of the dissolved tablet to a desirable consistency and improve its overall texture and bite and help facilitate the release of the therapeutic agent. Non-limiting examples of such plasticizers are discussed in detail above and may be used alone or in combination in the tablet compositions of the present invention.

In certain instances, the tablet composition includes a therapeutic agent centerfill, e.g., as described above. In certain other instances, the tablet composition of the present invention is multilayered. In this way, the dissolving or chewable tablet can be designed to provide more than one therapeutic agent. For example, with a bi-layered tablet, the first layer can contain zolpidem or a salt thereof and the second layer can contain the same or different hypnotic agent or a non-hypnotic agent. Typically, the first layer comprises the dissolving or chewable portion of the tablet, and the second (i.e., subsequent) layer is coated by the first layer. This type of formulation may be particularly suitable when immediate release of zolpidem, followed by gastrointestinal absorption of a second therapeutic agent, is desirable. Gastrointestinal absorption of the second therapeutic agent may be desirable, for example, in order to mitigate co-morbid symptoms or to sustain the therapeutic benefit of zolpidem in the dissolving or the chewable portion of the tablet. Alternatively, the second layer is present as a layer lateral to the first layer. The second layer typically comprises at least one therapeutic agent, and can also comprise one or more sweetening agents, flavoring agents, coloring agents, and scenting agents as described above. In some instances, the second layer further includes a buffer system as described herein.

In still other instances, the combination of zolpidem or a salt thereof with other hypnotic agents and/or non-hypnotic agents need not take the form of a multilayered tablet, but

instead comprises a single homogenous tablet layer. This type of formulation may also be used in the case where gastrointestinal absorption of at least one therapeutic agent is desirable. In this case, the relative extent of ionization of the two or more therapeutic agents determines how they are to be absorbed. For example, those therapeutic agents that are un-ionized are absorbed through the oral mucosa, while the ionized agents are swallowed for gastrointestinal absorption.

The tablet compositions can have any desired shape, size, and texture. For example, the tablet can have the shape of a stick, tab, pellet, sphere, and the like. Similarly, the tablet can be any desirable color. For example, the tablet can be any shade of red, blue, green, orange, yellow, violet, indigo, and mixtures thereof, and can be color coded to indicate the type and dosage of the therapeutic agent therein. The tablets can be individually wrapped or grouped together in pieces for packaging by methods well known in the art.

When the dosage form is a lozenge or candy, the composition can comprise zolpidem or a pharmaceutically acceptable salt thereof, a carrier or excipient such as a binder, and a pH-adjusting agent or buffer system. The lozenge or candy composition may further comprise protecting agents, lubricating agents, wetting agents, emulsifying agents, solubilizing agents; suspending agents, preserving agents, sweetening agents, flavoring agents, coloring agents, and disintegrating agents. A general discussion of lozenges and candies is provided, e.g., in *Pharmaceutical Dosage Forms, Volume 1: Tablets,* 2nd Ed., Marcel Dekker, Inc., New York, N.Y., pages 75-418 (1989). Typically, the lozenge compositions of the present invention comprise less than about 5 mg (e.g., from about 0.5 mg to about 4.75 mg, from about 1.5 mg to about 2.5 mg, from about 3.0 mg to about 3.75 mg, etc.) of zolpidem or a salt thereof. One skilled in the art understands that the foregoing amounts will vary depending upon the particular source of zolpidem utilized, the amount of zolpidem desired in the final formulation, as well as on the particular release rate of zolpidem desired. In certain instances, the buffer system of the lozenge compositions provides a final salivary pH in excess of at least about 7.8, preferably at least about 8.5, and more preferably at least about 9 (e.g., about 9-11).

In certain embodiments, the lozenge or candy is dissolved by a subject's saliva, without the need for chewing. For example, a lozenge placed on the subject's tongue can be used for buccal delivery of the therapeutic agent. Alternatively, a lozenge placed underneath the subject's tongue can be used for sublingual delivery of the therapeutic agent. This type of dosage form may be particularly desirable for pediatric and geriatric patients, since small children and aged individuals often have difficulty chewing certain items. Typically, the lozenge is formulated to dissolve within about 1 to about 15 minutes, preferably within about 2 to about 10 minutes, e.g., within about 2, 3, 4, 5, 6, 7, 8, 9, or 10 minutes, following administration. In a preferred embodiment, the lozenge or candy delivers the therapeutic agent across the sublingual mucosa.

As described above, the lozenges the present invention are typically formulated to dissolve within about 1 to about 15 minutes following administration. However, while these time frames are amenable to maximum exposure of the therapeutic agent to the oral mucosa (e.g., to the sublingual and/or buccal mucosa), they are not always amenable to user compliance (e.g., users may swallow too frequently and, therefore, hinder maximal transmucosal absorption). Consequently, in certain instances, it may be desirable to strike a balance between patient compliance and maximum exposure time of the therapeutic agent to the oral mucosa. This can be accomplished, for example, by reducing the lozenge size (e.g., from about 700-800 mg to about 200-300 mg or about 100-350 mg) without reducing the concentration or amount per unit dose of the buffer system or the therapeutic agent. In addition, subtle changes to the lozenge formulation such as, for example, replacing one flavoring agent for another (e.g., chocolate for spearmint) or replacing one binder or sweetening agent for another (e.g., lactose for mannitol or sorbitol) may be used to reduce salivation.

The carrier or excipient present in the lozenges of the present invention is typically a binder that is useful in keeping the lozenge in a semi-solid state, and may be a solid or a liquid, and may for example be a high-melting point fat or waxy material. Materials suitable as binders are discussed in detail above and may be used alone or in combination in the lozenge compositions of the present invention. In addition, binders such as mannitol, sorbitol, lactose, sucrose, and inositol can impart properties to the lozenge that permit or enhance its disintegration in the mouth.

The lozenge composition may also comprise one or more elastomeric solvents such as rosins and resins. Non-limiting examples of such solvents are discussed in detail above and may be used alone or in combination in the lozenge compositions of the present invention. In addition, the lozenge composition may further comprise waxes such as beeswax and microcrystalline wax, fats, or oils such as soybean and cottonseed oil, and combinations thereof. Moreover, the lozenge composition may additionally include plasticizers such as softeners or emulsifiers. Such plasticizers may, for example, help reduce the viscosity of the salivary solution of the dissolved lozenge to a desirable consistency and improve its overall texture and bite and help facilitate the release of the therapeutic agent. Non-limiting examples of such plasticizers are discussed in detail above and may be used alone or in combination in the lozenge compositions of the present invention.

In other embodiments, the lozenge composition includes a therapeutic agent centerfill, is multilayered, or comprises a single homogenous lozenge layer, e.g., as described in detail above.

The lozenge compositions can have any desired shape, size, and texture. For example, the lozenge can have the shape of a stick, tab, pellet, sphere, and the like. Similarly, the lozenge can be any desirable color. For example, the lozenge can be any shade of red, blue, green, orange, yellow, violet, indigo, and mixtures thereof, and can be color coded to indicate the type and dosage of the therapeutic agent therein. The lozenges can be individually wrapped or grouped together in pieces for packaging by methods well known in the art.

In a preferred embodiment, the average particle size of the drug in the compositions described herein is about 20 microns, as compared to a typical average drug particle size of from about 75 to about 100 microns. In another preferred embodiment, the average particle size of the drug in the compositions described herein is less than or equal to the average particle size of the carrier ingredients (e.g., gum base, binders, etc.).

Typically, the pharmaceutical compositions are suitable for buccal or sublingual administration of zolpidem in the low doses provided herein. Compositions suitable for buccal or sublingual administration of zolpidem are those that provide absorption in the buccal cavity of at least about 10%, 20%, or 25% of the dosage of zolpidem in the composition. This amount is generally at least twice the amount of buccal absorption that could be expected for a tablet designed to be swallowed for absorption of the active agent in the gut. Additionally, the time to C_{max} is reduced for such compositions relative to tablets or capsules designed to deliver zolpidem in

the gut. The compositions suitable for buccal or sublingual administration of zolpidem in low doses, as noted above, are sufficient to reduce the time to C_{max}, enhancing the early effect of zolpidem and increase plasma levels of zolpidem, generally two-fold or more during the first 20 minutes after administration, relative to tablets or capsules designed for delivery in the gut (e.g., to be swallowed immediately upon ingestion).

Typically, the compositions that are suitable for the treatment of MOTN insomnia following buccal or sublingual administration have a unique and discriminatory dissolution profile. Such a dissolution method relies on modified USP method II dissolution procedure and where the pH of the dissolution medium is 6.8, which approximates the pH of the saliva. The method is considered to be a modification as the volume of the medium is reduced to 500 ml from 1 liter and the paddle speed for dissolution is reduced to 15 rpm from a typical speed of 50 or more rpm. This method is sufficiently sensitive to discriminate a 2 to 3 minute dissolution tablet from a tablet that would normally take 5 minutes or more to dissolve in the mouth. Typically, a tablet that would dissolve in the mouth in 3 minutes or less would dissolve more rapidly under experimental conditions of modified USP method II than a tablet that takes 5 or more minutes to dissolve in the mouth (see, Tables 1-2 below)

TABLE 1

Exploratory dissolution profiles of 3 and 5 minute dissolution of zolpidem lozenges using the modified USP dissolution method II. (500 ml of pH 6.8 phosphate buffer at a 37° C. and paddle speed of 15 rpm).

	Lozenge			
	"3 minute" dissolution prototype		"5 minute" dissolution prototype	
Time (min)	Dissolution	RSD*	Dissolution	RSD*
5	28.60%	5%	8.70%	12.00%
10	58.40%	10%	20.00%	11.30%
20	79.00%	20%	38.30%	11.40%

*Relative standard deviation

TABLE 2

Illustrative dissolution profiles of 1, 3.5, and 10 mg "3 minute" zolpidem lozenges using the modified USP dissolution method II. (500 ml of pH 6.8 phosphate buffer at a 37° C. and paddle speed of 15 rpm).

Lozenge	1 mg "3 minute" dissolution prototype		3.5 mg "3 minute" dissolution prototype		10 mg "3 minute" dissolution prototype	
Time (min)	Dissolution	RSD	Dissolution	RSD	Dissolution	RSD
5	28.70%	11.60%	42.40%	11.14%	28.60%	19.90%
10	46.90%	9.30%	70.20%	6.53%	58.40%	10.40%
15	60.40%	6.70%	81.00%	7.23%		
20	70.50%	5.20%	84.30%	7.14%	79.00%	5.10%

In some embodiments, the compositions of the present invention provide complete buccal and/or sublingual dissolution in about 2 minutes or less following administration. The quick-dissolving tablets of the present invention usually provide complete buccal and/or sublingual dissolution in less than about 0.5 minutes, alternatively in less than about 1 minute, alternatively in less than about 1.5 minutes, alternatively in less than about 2 minutes, alternatively in less than about 2.5 minutes, alternatively in less than about 3 minutes, alternatively in less than about 4 minutes, alternatively in less than about 5 minutes, or alternatively in less than about 6 minutes.

Generally, the compositions described herein comprise a binary or a ternary buffer system, the system comprised of at least one proton donating (acidic) component and at least one proton accepting (basic) component. The components of the buffer system are selected such that their buffering capacity is greatest (the buffer system has a pK value) at a pH of from about 7.2-11.0, usually at a pH of about, for example, 7.2, 7.6, 7.8, 8.0, 8.3, 8.5, 8.8, 9.0, 9.4, 9.5, 9.6, 9.7, or 9.8.

In preferred embodiments, the binary buffer system raises the pH of saliva to a pH greater than about 7.2, 7.6, 7.8, 8.0, 8.3, 8.5, or 8.8, irrespective of the starting pH of saliva. In other embodiments, the binary buffer system raises the pH of saliva to a pH greater than about 9.0, 9.4, 9.5, 9.6, 9.7, or 9.8 (e.g., about 9-11), irrespective of the starting pH of saliva.

Preferably, the buffer system comprises a carbonate and a bicarbonate component. For example, the carbonate salt can be selected from the group consisting of sodium carbonate, potassium carbonate, calcium carbonate, ammonium carbonate, and magnesium carbonate. The bicarbonate salt can be selected from the group consisting of sodium bicarbonate, potassium bicarbonate, calcium bicarbonate, ammonium bicarbonate, and magnesium bicarbonate. In a preferred embodiment, the binary buffer system comprises sodium carbonate and sodium bicarbonate. In another preferred embodiment, the sodium bicarbonate is dessicant-coated sodium bicarbonate. The cations of the carbonate and the bicarbonate components can be the same or different.

The concentration of each buffer system component is tailored such that the final salivary pH is achieved and sustained for a period of time, e.g., for at least about 2 minutes, at least about 5 minutes, at least about 10 minutes, at least about 20 minutes, or at least about 60 minutes. This typically involves a sensory and safety trial and error type of procedure of adding various amounts of each buffer system component and then measuring the final pH over time. In this way, selection of an appropriate weight ratio for each buffer system component can be determined. For example, the weight ratio of carbonate salt to bicarbonate salt can be from about 1:10 to about 10:1, preferably from about 1:5 to about 5:1, more preferably from about 1:4 to about 4:1 or from about 1:3 to about 3:1, and still more preferably from about 1:2 to about 2:1.

In some embodiments, the amount of bicarbonate salt is greater than or equal to the amount of carbonate salt, and the weight ratio of carbonate salt to bicarbonate salt is from about 1:1 to about 1:10, preferably from about 1:1 to about 1:5, and more preferably from about 1:1 to about 1:2, e.g., 1:1, 1:1.1, 1:1.2, 1:1.3, 1:1.4, 1:1.5, 1:1.6, 1:1.7, 1:1.8, 1:1.9, or 1:2.

Alternatively, the amount of bicarbonate salt is less than or equal to the amount of carbonate salt, and the weight ratio of carbonate salt to bicarbonate salt is from about 1:1 to about 10:1, preferably from about 1:1 to about 5:1, and more preferably from about 1:1 to about 2:1, e.g., 1:1, 1.1:1, 1.2:1, 1.3:1, 1.4:1, 1.5:1, 1.6:1, 1.7:1, 1.8:1, 1.9:1, or 2:1. In some embodiments, the combined amount of carbonate salt and bicarbonate salt is greater than or equal to the amount of zolpidem, and the weight ratio of carbonate salt and bicarbonate salt to zolpidem is preferably from about 1:1 to about 10:1, e.g., 1:1, 2:1, 3:1, 4:1, 5:1, 6:1, 7:1, 8:1, 9:1, or 10:1. Alternatively, the combined amount of carbonate salt and bicarbonate salt is less than or equal to the amount of zolpidem, and the weight ratio of carbonate salt and bicarbonate salt to zolpidem is preferably from about 1:1 to about 1:10, e.g., 1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, 1:8, 1:9, or 1:10.

In some embodiments, the binary buffer system used in compositions described above comprises a carbonate salt such as sodium carbonate and a bicarbonate salt such as sodium bicarbonate, wherein the carbonate salt and the bicarbonate salt are in a carbonate:bicarbonate ratio of from about 1:1.0 to about 1:1.4 by weight, or alternatively from about 1:1.0 to about 1:1.2 by weight.

In other embodiments, the bicarbonate can be used by itself to promote selective absorption of zolpidem.

Other buffer systems are suitable for use in the compositions of the present invention, in addition to or in substitution of a carbonate and bicarbonate buffer system. For example, in an alternative embodiment, the buffer system comprises a carbonate salt or a bicarbonate salt and a second buffering agent such as a metal oxide, a citrate salt, a phosphate salt, a borate salt, an ascorbate salt, an acetate salt, and alkaline starch. In another alternative embodiment, the buffer system comprises a metal oxide and a citrate, phosphate, or borate salt. In yet another alternative embodiment, the buffer system is a ternary buffer system comprising a carbonate salt, a bicarbonate salt, and a third buffering agent such as a metal oxide, a citrate salt, a phosphate salt, a borate salt, an ascorbate salt, an acetate salt, and alkaline starch. In still yet another alternative embodiment, the buffer system comprises a carbonate salt or a bicarbonate salt and two or more buffering agents selected from the group consisting of a metal oxide, a citrate salt, a phosphate salt, and a borate salt.

In still other embodiments, the pharmaceutical compositions comprise a carrier comprising at least one binder and at least one disintegrating agent in such relative proportion to provide a buccal or sublingual dissolution time of about 5 minutes or less, preferably about 2 minutes or less, following administration. Preferably, the ratio of the binder to the disintegrating agent is from about 0.1 to about 10.0, more preferably from about 0.1 to about 1.0, and most preferably from about 0.26 to about 0.79. However, one skilled in the art will appreciate that the compositions of the present invention can be made without any binders, e.g., to produce a highly friable dosage form.

In a preferred embodiment, the zolpidem is delivered across an oral mucosa selected from the group consisting of the sublingual mucosa, the buccal mucosa, and a combination thereof. In a particularly preferred embodiment, the composition is administered sublingually so that the zolpidem is delivered across the sublingual mucosa.

In preferred embodiments of the present invention, the zolpidem is formulated in a binary buffer system comprising sodium carbonate and sodium bicarbonate. Such compositions are preferably formulated in the form of a lozenge, candy, or dissolving tablet (e.g., slow-dissolving tablet or quick-dissolving tablet) for sublingual administration. As a result, upon sublingual administration, zolpidem is delivered across the sublingual mucosa. In another preferred embodiment, the sodium bicarbonate is dessicant-coated sodium bicarbonate. A combined weight percent of sodium carbonate and sodium bicarbonate that is greater than or equal to the weight percent of zolpidem is also preferred.

In some embodiments, the composition comprises from about 0.4, 0.45, or 0.5 to about 1.5, 1.6, 1.7, or 1.8 weight percent zolpidem; from about 6.0 to about 10.0 weight percent sodium carbonate; and from about 9.0 to about 13.0 weight percent dessicant-coated sodium bicarbonate. In a preferred embodiment, the composition comprises about 0.47, 0.8, or 1.7 weight percent zolpidem; about 8.0 weight percent sodium carbonate; and about 11.0 weight percent dessicant-coated sodium bicarbonate. Such compositions are preferably in the form of a lozenge or candy with a mass of from about 100 to about 300 mg, e.g., about 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, and 300 mg. The lozenges or tablets dissolve in a subject's mouth at a very rapid rate, e.g., within about 2-3 minutes following administration.

In certain other instances, the composition comprises from about 0.4, 0.45, or 0.5 to about 1.5, 1.6, 1.7, or 1.8 weight percent zolpidem; from about 5.0 to about 9.0 weight percent sodium carbonate; and from about 7.0 to about 11.0 weight percent sodium bicarbonate. In a preferred embodiment, the composition comprises about 0.47, 0.8, or 1.7 weight percent zolpidem; about 7.0 weight percent sodium carbonate; and about 9.0 weight percent sodium bicarbonate. Such compositions are preferably in the form of a dissolving tablet such as a slow-dissolving tablet or a quick-dissolving tablet of from about 100 to about 300 mg, e.g., about 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, and 300 mg. The quick-dissolving tablets dissolve in a subject's mouth at a rapid rate, e.g., within about 5 minutes following administration, and the slow-dissolving tablets dissolve in a subject's mouth at a slower rate, e.g., within about 10 minutes following administration.

V. Methods

In carrying out the methods of the present invention for treating MOTN insomnia, the appropriate effective dosage to be administered to a subject can be evaluated in an appropriate patient population that has been selected based on factors such as age, weight, the number of hours of time in bed remaining, and/or the ability of a subject to metabolize zolpidem. For example, a dose of about 2 mg to about 5 mg can be administered to a subject who awakens and still has about 4 or 5 hours of time in bed remaining. Similarly, a dose of about 3 mg to about 5 mg can be administered to non-elderly subjects (i.e., subjects younger than 65 years of age) with a normal capacity to metabolize zolpidem. If the subject awakens with about 2-4 hours of time in bed remaining, a dose of about 0.5 mg to about 2.5 mg can be administered. Likewise, subjects with a diminished capacity to metabolize zolpidem (i.e., subjects 65 years of age and older) can be administered a portion of a dose that would be administered to a subject with a normal capacity to metabolize zolpidem, for example, a half-tablet dose. One of skill in the art will appreciate that there can be some variability in the dose provided to some individuals. For example, hepatically-impaired individuals may use a very low dose such as that typically provided for an elderly patient.

Typically, an effective amount of zolpidem is administered to a subject with MOTN insomnia on an as needed basis, i.e., pro re nata. That is, the individual had previously fallen asleep, and the sleep time has been interrupted with at least

about 2, 3, 4, or 5 hours of time in bed remaining. Generally, in practicing the present methods, zolpidem is not administered prophylactically, or before initial onset of sleep.

Typically, the methods are carried out by administering a composition of the present invention as described above. Compositions of particular interest for treating MOTN insomnia contain less than about 5 mg of zolpidem or a salt thereof. In certain embodiments, the zolpidem can be administered in a quick-dissolving tablet or lozenge. Efficient delivery of zolpidem can be achieved using a formulation with a binary or a ternary buffer system, for example with carbonate and bicarbonate components, as described above.

Administration of the compositions of the present invention is preferably carried out via any of the accepted modes of administration to the mucous membranes of the oral cavity. Examples of suitable sites of administration within the oral mucosa include, without limitation, the mucous membranes of the floor of the mouth (sublingual mucosa), the cheeks (buccal mucosa), the gums (gingival mucosa), the roof of the mouth (palatal mucosa), the lining of the lips, and combinations thereof. These regions differ from each other with respect to their anatomy, drug permeability, and physiological response to drugs. Preferably, the compositions of the present invention are administered to the sublingual mucosa, buccal mucosa, or a combination thereof.

The oral mucosa, possessing a rich blood supply and suitable drug permeability, is an especially attractive route of administration for systemic drug delivery. Furthermore, delivery of a therapeutic agent across the oral mucosa bypasses hepatic first pass metabolism, avoids enzymatic degradation within the gastrointestinal tract, and provides a more suitable enzymatic flora for drug absorption. As used herein, the term "sublingual delivery" refers to the administration of a therapeutic agent across the mucous membranes lining the floor of the mouth and/or the ventral tongue. The term "buccal delivery" as used herein refers to the administration of a therapeutic agent across the mucous membranes lining the cheeks.

VI. Examples

The following examples are offered to illustrate, but not to limit, the claimed invention.

Example 1

Low Dose Zolpidem Lozenge Compositions

Individuals suffering from middle-of-the-night insomnia are given lozenges containing 0 mg, 1.0 mg, 1.75 mg, or 3.5 mg zolpidem for sublingual delivery that are prepared according to the formulations set forth in Table 3.

TABLE 3

Low dose zolpidem lozenge formulations.

	Quantity (mg/lozenge) Strength				
Component	Placebo	1.0 mg	1.75 mg	1.75 mg	3.5 mg
Zolpidem hemitartrate	0	1.0	1.75	1.75	3.5
Pharmaburst ™ B2 Consisting of: mannitol sorbitol crospovidone silicon dioxide	143	142	70	141.25	139.5

TABLE 3-continued

Low dose zolpidem lozenge formulations.

	Quantity (mg/lozenge) Strength				
Component	Placebo	1.0 mg	1.75 mg	1.75 mg	3.5 mg
Croscarmellose sodium	10	10	5	10	10
Sodium carbonate	17	17	8.5	17	17
Sodium bicarbonate	23	23	11.5	23	23
Natural and artificial spearmint FONA# 913.004	6.5	6.5	3.25	6.5	6.5
Silicon dioxide	5.5	5.5	2.75	5.5	5.5
Sucralose	1.5	1.5	0.75	1.5	1.5
Magnesium stearate	3.5	3.5	1.75	3.5	3.5
Total lozenge weight	210	210	105	210	210

The individuals self-administer one lozenge of the above formulations when their sleep is interrupted and they have at least 2 hours of sleep time remaining. Upon awakening, the individuals provide a subjective self-assessment of any residual sedative effects and are given the following psychomotor and memory tests to evaluate any residual sedative effects: a digit symbol substitution test (DSST), a choice reaction time (CRT), a symbol copy test (SCT), and a Buschke Memory Recall Test.

Individuals receiving a placebo lozenge are generally unable to fall back asleep and therefore do not feel refreshed in the morning. Individuals receiving lozenges containing 1.0 mg, 1.75 mg, or 3.5 mg zolpidem fall asleep within about 20 minutes after self-administration of the lozenge and exhibit no or minimal residual sedative effects as evaluated by subjective self-assessment and any of the above-referenced psychomotor and memory tests.

Example 2

Pharmacokinetic and Pharmacodynamic Investigation of Low Dose Zolpidem Lozenge Compositions

This example provides an evaluation of the daytime dose-dependent pharmacokinetic and pharmacodynamic effects of the 1.0 mg, 1.75 mg, and 3.5 mg zolpidem lozenges described in Table 3 above.

SUMMARY

Currently, no medications are available to be used on a pro re nata basis for patients who have middle-of-the-night (MOTN) awakening and who have difficulty falling back asleep. An appropriate therapeutic agent for such insomnia would enable patients to return to sleep rapidly and wake up in the morning without residual effects. This study illustrates, inter alis, that the low dose zolpidem lozenges of the present invention enhance rapid systemic delivery of zolpidem without affecting other pharmacokinetic parameters.

Healthy adults (n=24; mean age=37.6 yrs) participated in this double-blind, placebo-controlled, 4-way crossover study of 2 consecutive days of morning dosing with placebo, or 1 mg, 1.75 mg, or 3.5 mg of the low dose zolpidem lozenges of the present invention. After morning dosing, on Day 1 of each period, pharmacodynamic endpoints (DSST, PVT, VAS-sedation, SCT, and Buschke) were evaluated at pre-dose and at 20 minutes 1, 1.5, 2, 3, 4, and 5 hours post-dose. On Day 2, repeated blood samples for pharmacokinetic assessment were drawn over 12 hours.

Baseline DSST scores (±SE) were 57.6±2.9, 58.0±3.1, 58.4±2.3, and 56.9±2.7 for the placebo, 1 mg, 1.75 mg, and 3.5 mg zolpidem lozenge, respectively. Significant reductions in DSST, scores were found for the 1.75 mg and 3.5 mg zolpidem lozenges at the beginning of 20 minutes (−6.6; p=0.0132 and −14.8; p<0.001, respectively) and lasted for 1.5 hours post-dose. Other endpoints showed results similar to DSST. Mean T_{max} was 36.0, 37.9, and 37.9 minutes for the 1 mg, 1.75 mg, and 3.5 mg zolpidem lozenge, respectively. Zolpidem C_{max} and AUC were dose-proportional. The 1.75 mg and 3.5 mg zolpidem lozenges reached sedation plasma levels (about 20 ng/ml) within 15 minutes, and these levels were maintained for 15 to 240 minutes.

Low dose zolpidem lozenges provide daytime sedative properties at a dose and a T_{max} of less than half of the approved dose of peroral (PO) zolpidem (10 mg) in adults. This study demonstrates that the low dose sublingual zolpidem lozenges of the present invention can be used to shorten sleep onset upon MOTN administration.

Methods

Design

This was a four-way crossover, placebo controlled, randomized double blind study with healthy male (n=13) and female (n=11) volunteers. Each treatment period consisted of two single-dose consecutive treatment days, and each treatment was separated by a wash-out period of 6 days or more. During each period, lozenges were administered approximately 24 hours apart, and the subjects received the same treatment on each day. During each period, in order to avoid any learning or drug-anticipatory response, the pharmacodynamic effects were measured on Day 1 and blood samples drawn on Day 2 for pharmacokinetic assessment.

Pharmacodynamic assessment consisted of measurements of sedation, memory, and vigilance tests. The sedative effects were quantified by a decrease in post- to pre-dose scores on a Digit Symbol Substitution Test (DSST) and self-rated assessment sedation on a Visual Analog Scale (VAS). Vigilance was assessed by an increase in post- to pre-dose scores by measurement of reaction time and number of lapses in reaction to digital stimuli using a computerized Psychomotor Vigilance Test (PVT). A decrease in post- to pre-dose scores on a Buschke Word Recall Test (Buschke) was used for memory effects. Additionally, a Symbol Copy Test (SCT) was used for measurement of simple cognitive function. The results were statistically analyzed using SAS, ANOVA procedures and significance was assessed using Dunnett's test for comparison.

Serial blood samples were drawn for up to 12 hours at pre-dose, 5, 10, 20, 30, and 45 minutes and 1, 2, 2.5, 3, 3.5, 4, 5, 6, 8, and 12 hours. Non-compartmental pharmacokinetic parameters were estimated using the WinNonlin program (Pharsight Corp.; Palo Alto, Calif.). The parameters estimated were AUC and partial AUC, C_{max}, t_{max}, and $t_{1/2}$.

Additionally, the plasma levels of the 1.0 mg, 1.75 mg, and 3.5 mg zolpidem lozenges were predicted following single compartment first order input and output modeling of data for a 10 mg zolpidem lozenge using the following equation:

$$Ct=D*K01/V/(K01-K10)*EXP(-K10*T)-EXP(-K01*T),$$

wherein Ct=predicted plasma concentration, D=dose, V=apparent volume of distribution, T=time, K01=absorption rate constant, and K10=the elimination rate constant. The values for V, K01 and K10 were obtained by fitting the plasma data from the 10 mg zolpidem lozenge (i.e., 3 minute dissolution lozenge swallowed every 2 minutes) to the above equation. Unless otherwise indicated, standard deviation is the variance parameter associated with the mean values.

Results

Pharmacokinetics

Zolpidem was rapidly absorbed and eliminated from each of the three low dose sublingual lozenge formulations. The plasma profiles of the three lozenge formulations are shown in FIG. **1**, and summary statistics of the pharmacokinetic parameters are described in Table 4. Overall, the t_{max} and C_{max} of the three lozenge formulations were significantly shorter and higher, respectively, than the values either predicted by modeling of the 10 mg data (see, FIG. **2**) or reported in the literature.

TABLE 4

Mean (% CV) bioavailability arameters of the low dose zol idem lozen es.

Dose mg	C_{max} ng/ml	t_{max} min	AUC 0-12 hr ng · hr/ml	AUC 0-20 mn ng · hr/ml	Mean Bioavailability Rate (ng/ml per min)
1.0	17.77 (33%)	36 (30%)	65.31 (40%)	1.53 (42%)	0.49
1.75	32.17 (32%)	37.9 (42%)	119.54 (40%)	3.20 (42%)	0.85
3.5	64.14 (33%)	37.9 (40%)	229.42 (40%)	5.80 (41%)	1.69

In particular, this pharmacokinetic study provided the following key observations:

1. The 3.5 mg lozenge produced a C_{max} of about 64 ng/ml in about 38 minutes with an AUC0-12 hr of about 229 ng·hr/ml. The mean value AUC0-20 min was 5.80 ng·hr/ml.
2. The values of the C_{max} and t_{max} for the 1.75 mg lozenge were about 32 ng/ml and 38 minutes, respectively. The values of AUC0-12 hr and AUC0-20 min were 119.54 and 3.20 ng·hr/ml, respectively.
3. The values of the C_{max} and t_{max} for the 1 mg lozenge were about 18 ng/ml and 36 minutes, respectively. The values of AUC0-12 hr and AUC0-20 min were 65.31 and 1.53 ng·hr/ml, respectively.
4. The observed values of C_{max} of all three lozenge formulations were significantly higher than the values predicted by pharmacokinetic modeling of the 10 mg data.
5. The pharmacokinetics of the three lozenge formulations were proportional to the dose.

Pharmacodynamics

Digit Symbol Substitution Test (DSST): The DSST is an objective measure of sedation. As shown in FIG. **3**, the 1.75 mg and 3.5 mg zolpidem lozenges produced peak changes in DSST scores within 20 to 60 minutes of administration, and scores returned to baseline within 3 to 4 hours of administration. These scores were significantly different from baseline for up to about 90 minutes. The DSST scores for the 1 mg zolpidem lozenge were statistically similar to that of the placebo.

FIG. **4** shows that the relationship between plasma levels of the zolpidem lozenges and the DSST response is characterized by an anti-clockwise hysteresis loop, which is typical for sedative-hypnotics. This indicates that the rapid pharmacodynamic effects are primarily due to the rapid bioavailability of the zolpidem present in the lozenges and not due to any changes in the receptor pharmacology of the drug.

One of the most surprising findings from the DSST scores for the 3.5 mg zolpidem lozenge is that the sedative response is more rapid than the values reported in the literature for 5 mg

and 10 mg peroral (PO) Ambien® (see, Greenblatt et al., *Clin. Pharmacol. Therap.,* 64:553-561 (1998); Greenblatt et al., *Clin. Pharmacol. Therap.,* 64:661-671 (1998)). In particular, FIG. **5** shows that the 3.5 mg zolpidem lozenge was capable of inducing sleep more rapidly than both 5 mg and 10 mg PO Ambien®, but did not cause the excessive sedation associated with 10 mg PO Ambien®.

Self-rated assessment of sedation on VAS: Unlike DSST, the subjective sedative effects of the 1.75 mg and 3.5 mg zolpidem lozenges were similar (FIG. **6**). The Visual Analog Scale (VAS) scores for these low zolpidem doses were statistically different than placebo for up to 2 hours.

Vigilance changes as measured by PVT: The 3.5 mg zolpidem lozenge also impaired vigilance, as measured by reaction times using a Psychomotor Vigilance Test (PVT). FIG. **7** shows that the reaction time scores for the 3.5 mg zolpidem lozenge were statistically different for up to about 90 minutes.

Memory impairment (Buschke): Except for the significant effect seen at 20 minutes with the 3.5 mg zolpidem lozenge, the drug effects were comparable to that of the placebo.

Simple motor task impairment (SCT): The effects of the three lozenge formulations were comparable to that of the placebo.

CONCLUSIONS

1. Surprisingly, the zolpidem blood levels established at several time points up to 30 mintues after dosing with the 3.5 mg zolpidem lozenge exceeded those reported in the literature for PO Ambien® doses up to and including 10 mg. In fact, the 3.5 mg zolpidem lozenge was superior to 10 mg PO Ambien® (which contains nearly 3 times the dose of zolpidem) because it provided a significantly greater sedative effect at 30 minutes as measured by DSST testing.
2. The C_{max} (maximum plasma concentration) of zolpidem from the low dose zolpidem lozenges was about 30% higher than the values predicted by pharmacokinetic modeling of data for a 10 mg zolpidem lozenge. The mean C_{max} (64 ng/ml) of the 3.5 mg zolpidem lozenge was in the same range as the values reported for 5 mg PO Ambien®. Further, both 1.75 mg and 3.5 mg zolpidem lozenges produced plasma levels at 30 minutes or earlier that have been reported in the literature to produce sedative effects.
3. The low dose zolpidem lozenges achieved maximum plasma concentrations in about 36 to 38 minutes. A t_{max} of about 35 minutes was significantly earlier than the t_{max} of 1 to 1.5 hours typically reported for 5 mg and 10 mg PO zolpidem (Ambien®), eszopiclone (Lunesta™), zaleplon (Sonata®), and remelteon (Rozerem™)
4. The pharmacodynamic data described above demonstrate that the 1.75 mg and 3.5 mg zolpidem lozenges produced rapid sedative-hypnotic effects without the risk of anterograde amnesia or falling in night, which are side-effects typical of higher PO Ambien® doses.
5. The pharmacokinetic and pharmacodynamic response to the low dose zolpidem lozenges was proportional to the dose. Therefore, the pharmacology of zolpidem at a dose range of between about 1 mg to 3.5 mg, unlike that of 5 mg PO Ambien®, is expected to produce a consistent and predictable response.
6. The pharmacodynamic data described above clearly demonstrate the sedative effects of 1.75 mg and 3.5 mg zolpidem lozenge formulations, which included rapid onset of action. In fact, the onset of action and peak effects as defined by both DSST (objective) and VAS (subjective) occurred within 20 minutes. In contrast, 5 mg PO Ambien® produced peak DSST effects in about 60 minutes and the magnitude of the response was only about 50% of that seen with the 3.5 mg zolpidem lozenge. The levels of decline in DSST (surrogate for sedation) scores were comparable to those seen with marketed hypnotics.
7. During the pharmacodynamic portion of the study, low dose zolpidem lozenges containing 1.75 or 3.5 mg zolpidem produced peak sedative effects (as measured by DSST and VAS) within about 20 minutes of dosing.
8. The 3.5 mg zolpidem lozenge also impaired vigilance (as measured by reaction times on PVT). The 1.75 mg zolpidem lozenge had no effect on subjects who were non-elderly adults.
9. None of the doses of zolpidem present in the low dose zolpidem lozenges impaired performance on a memory test (Buschke) or a simple motor task capability test (SCT).

Example 3

Low Dose Zolpidem Tablet Composition

An immediate release peroral (PO) tablet containing a low dose of zolpidem can be prepared according to the formulation set forth in Table 5.

TABLE 5

Low dose zolpidem tablet formulation.

Component	Quantity (mg)
Zolpidem Hemitartrate	3.5
Povidone K29/32	15.0
Sodium Starch Glycolate (SSG)	7.5
Starch 1500	15.0
Lactose Fast Flow	82.0
Prosolv SMCC 90	65.5
Sodium bicarbonate	40
Magnesium Stearate	1.5
Total	230

Manufacturing Process

Dispensing: Screen the zolpidem hemitartrate and excipients through screen #30. Dispense the required quantities of each ingredient.

Blending:

1. Transfer the zolpidem hemitartrate and Povidone K 29/32 to a V-Shell blender and blend for 2 min.
2. Add SSG and Starch 1500 to Step 1 and blend for another 2 min.
3. Add Lactose Fast Flow and Prosolv SMCC 90 to Step 2 and blend for another 10 min.
4. Mix an equal amount of the blend from Step 3 with magnesium stearate or sodium stearyl fumarate and transfer the mixture back to the V-Shell blender via screen # 30. Blend for 3 min.

Compression: Compress the final blend from Step 4 on a rotary press to a target tablet weight of 210 mg.

All publications and patent applications cited in this specification are herein incorporated by reference as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference. Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

What is claimed is:

1. A method of treating middle-of-the-night insomnia in a non-elderly patient without prophylactically administering zolpidem, comprising:

dosing the patient with a pharmaceutical composition comprising about 0.5 to about 4.75 mg of zolpidem hemitartrate or a molar equivalent amount of a pharmaceutically acceptable form of zolpidem, wherein the pharmaceutical composition is substantially free of other hypnotic agents, wherein the patient awakens from sleep, and desires to resume sleep for less than 5 hours,

wherein the step of dosing the pharmaceutical composition is performed after the patient awakens from sleep, and

wherein the pharmaceutical composition permits the patient to awaken at a time about four hours after dosing without residual sedative effects.

2. The method of claim **1**, wherein the patient resumes sleep within 30 minutes.

3. The method of claim **1**, wherein about 50% of the maximum plasma concentration (C_{max}) of zolpidem is reached in the patient within about 30 minutes or less of dosing.

4. The method of claim **1**, Wherein the pharmaceutical composition comprises about 3.0 mg to about 3.75 mg of zolpidem hemitartrate.

5. The method of claim **1**, wherein the pharmaceutical composition provides delivery of zolpidem across the patient's oral mucosa.

6. The method of claim **1**, wherein the pharmaceutically acceptable form of zolpidem is a salt form of zolpidem.

7. The method of claim **1**, wherein the pharmaceutical composition further comprises sodium stearyl fumarate.

8. The method of claim **1**, wherein the pharmaceutical composition comprises about 3.5 mg of zolpidem hemitartrate.

9. The method of claim **4**, wherein the pharmaceutical composition provides delivery of zolpidem across the patient's oral mucosa.

10. The method of claim **8**, wherein the pharmaceutical composition provides delivery of zolpidem across the patient's oral mucosa.

11. The method of claim **1**, wherein the pharmaceutical composition is free of other hypnotic agents.

12. A method of treating middle-of-the-night insomnia in an elderly patient without prophylactically administering zolpidem, comprising:

dosing the patient with a pharmaceutical composition comprising about 1.5 to about 2.5 mg of zolpidem hemitartrate or a molar equivalent amount of a pharmaceutically acceptable form of zolpidem, wherein the pharmaceutical composition is substantially free of other hypnotic agents, wherein the patient awakens from sleep, and desires to resume sleep for less than 5 hours,

wherein the step of dosing the pharmaceutical composition is performed after the patient awakens from sleep, and

wherein the pharmaceutical composition permits the patient to awaken at a time about four hours after dosing without residual sedative effects.

13. The method of claim **12**, wherein the patient resumes sleep within 30 minutes.

14. The method of claim **12**, wherein about 50% of the maximum plasma concentration (C_{max}) of zolpidem is reached in the patient within about 30 minutes or less of dosing.

15. The method of claim **12**, wherein the pharmaceutical composition provides delivery of zolpidem across the patient's oral mucosa.

16. The method of claim **12**, wherein the pharmaceutically acceptable form of zolpidem is a salt form of zolpidem.

17. The method of claim **12**, wherein the pharmaceutical composition further comprises sodium stearyl fumarate.

18. The method of claim **12**, wherein the pharmaceutical composition comprises about 1.75 mg of zolpidem hemitartrate.

19. The of claim **18**, wherein the pharmaceutical composition provides delivery of zolpidem across the patient's oral mucosa.

20. The method of claim **12**, wherein the pharmaceutical composition is free of other hypnotic agents.

21. The method of claim **1**, wherein the patient has a normal capacity to metabolize zolpidem.

22. The method of claim **1**, wherein the pharmaceutical composition comprises about 3.5 mg of zolpidem hemitartrate, wherein the pharmaceutically acceptable form of zolpidem is a salt form of zolpidem, wherein the pharmaceutical composition is free of other hypnotic agents, wherein the pharmaceutical composition provides delivery of zolpidem across the patient's oral mucosa, and wherein the patient resumes sleep within 30 minutes.

23. The method of claim **22**, wherein about 50% of the maximum plasma concentration (C_{max}) of zolpidem is reached in the patient within about 30 minutes or less of dosing.

24. The method of claim **12**, wherein the pharmaceutical composition comprises about 1.75 mg of zolpidem hemitartrate, wherein the pharmaceutically acceptable form of zolpidem is a salt form of zolpidem, wherein the pharmaceutical composition is free of other hypnotic agents, wherein the pharmaceutical composition provides delivery of zolpidem across the patient's oral mucosa, and wherein the patient resumes sleep within 30 minutes.

25. The method of claim **24**, wherein about 50% of the maximum plasma concentration (C_{max}) of zolpidem is reached in the patient within about 30 minutes or less of dosing.

* * * * *

EXHIBIT C

US008252809B2

(12) **United States Patent**
Singh

(10) **Patent No.: US 8,252,809 B2**
(45) **Date of Patent: *Aug. 28, 2012**

(54) **COMPOSITIONS FOR TREATING INSOMNIA**

(75) Inventor: **Nikhilesh N. Singh**, Mill Valley, CA (US)

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 10 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **12/795,934**

(22) Filed: **Jun. 8, 2010**

(65) **Prior Publication Data**

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Related U.S. Application Data

(63) Continuation of application No. 11/606,640, filed on Nov. 29, 2006, now abandoned, which is a continuation-in-part of application No. PCT/US2006/020502, filed on May 23, 2006, and a continuation-in-part of application No. 11/439,873, filed on May 23, 2006, now abandoned, and a continuation-in-part of application No. 11/440,410, filed on May 23, 2006, now abandoned, and a continuation-in-part of application No. 11/439,874, filed on May 23, 2006, now abandoned, and a continuation-in-part of application No. 11/439,884, filed on May 23, 2006, now abandoned.

(60) Provisional application No. 60/788,249, filed on Mar. 31, 2006, provisional application No. 60/788,340, filed on Mar. 31, 2006, provisional application No. 60/741,673, filed on Dec. 1, 2005, provisional application No. 60/684,842, filed on May 25, 2005.

(51) **Int. Cl.**
A61K 31/44 (2006.01)

(52) **U.S. Cl.** **514/294**; 514/923

(58) **Field of Classification Search** 514/294, 514/923

See application file for complete search history.

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(57) **ABSTRACT**

The present invention provides compositions for treating middle-of-the-night insomnia without residual sedative effects upon awakening by administering low doses (about 5 mg or less) of zolpidem or a salt thereof.

26 Claims, 11 Drawing Sheets

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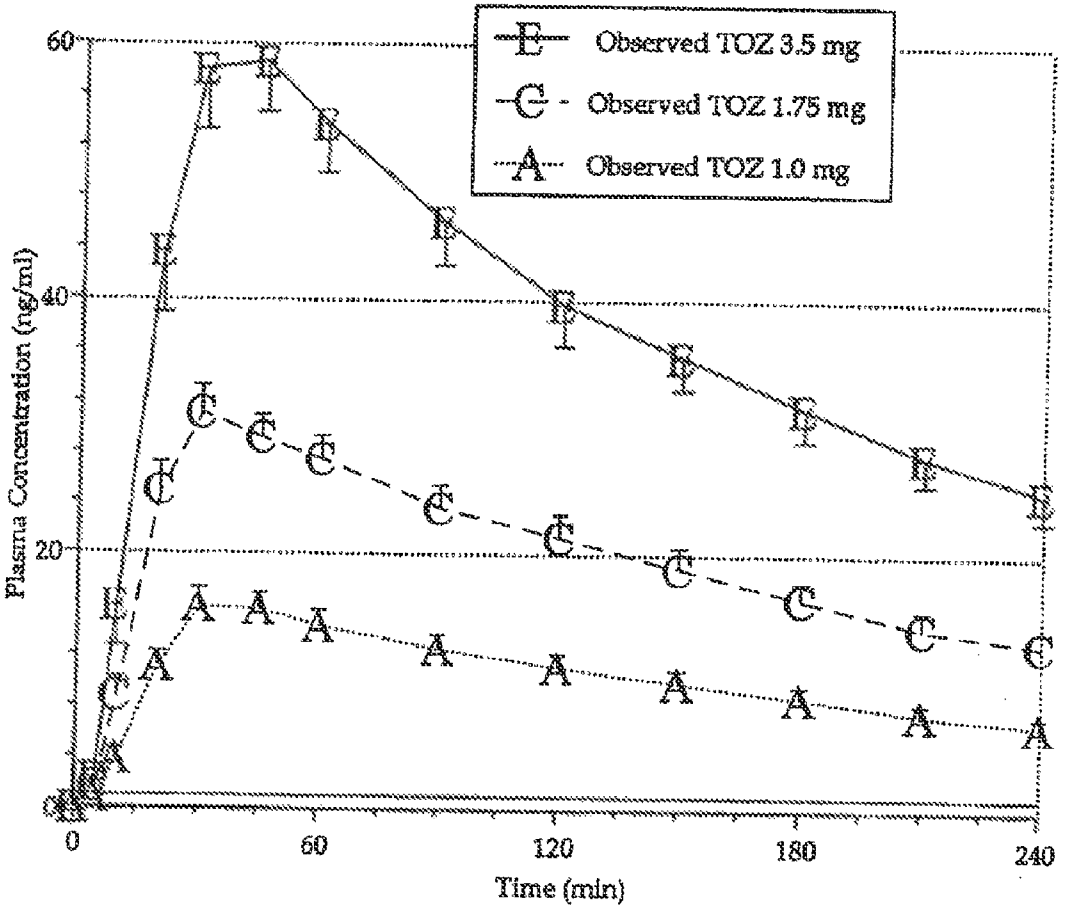
Observed TOZ 3.5 mg
Observed TOZ 1.75 mg
Observed TOZ 1.0 mg
Plasma Concentration (ng/ml)
60
40
20
0
0
60
120
180
240
Time (min)

FIG. 1

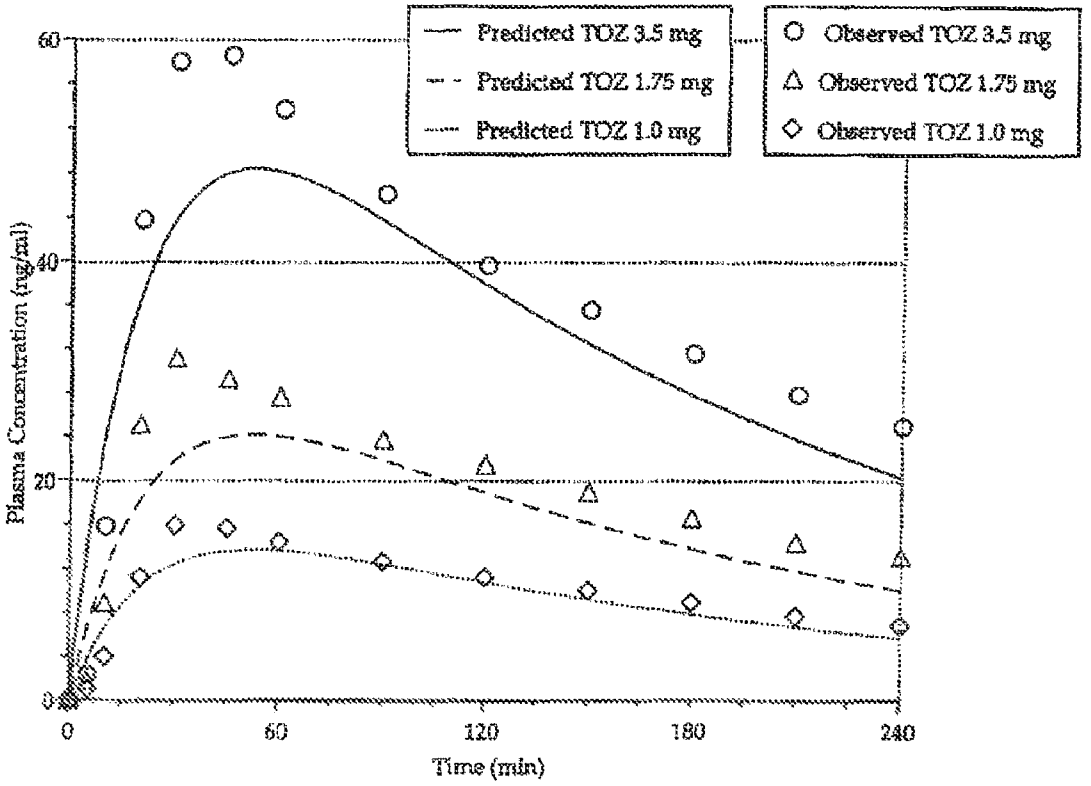
Predicted TOZ 3.5 mg
Predicted TOZ 1.75 mg
Predicted TOZ 1.0 mg
Observed TOZ 3.5 mg
Observed TOZ 1.75 mg
Observed TOZ 1.0 mg
Plasma Concentration (ng/ml)
60
40
20
0
0
60
120
180
240
Time (min)

FIG. 2

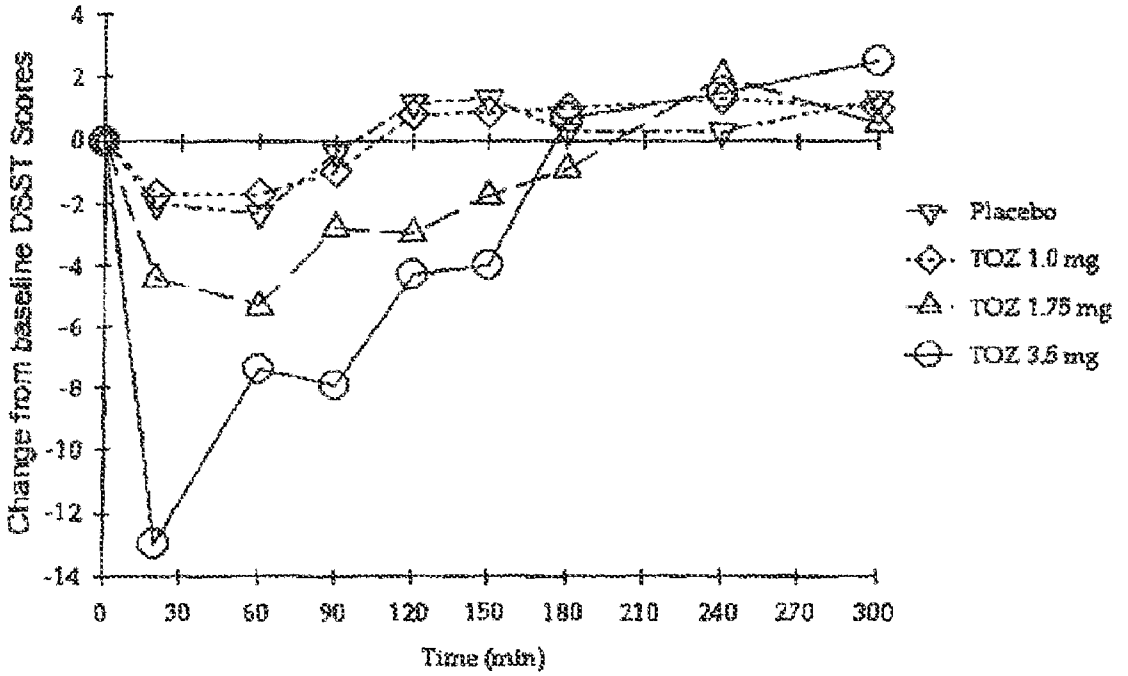
Change from baseline DSST Scores
4
2
0
-2
-4
-6
-8
-10
-12
-14
0
30
60
90
120
150
180
210
240
270
300
Time (min)
Placebo
TOZ 1.0 mg
TOZ 1.75 mg
TOZ 3.5 mg

FIG. 3

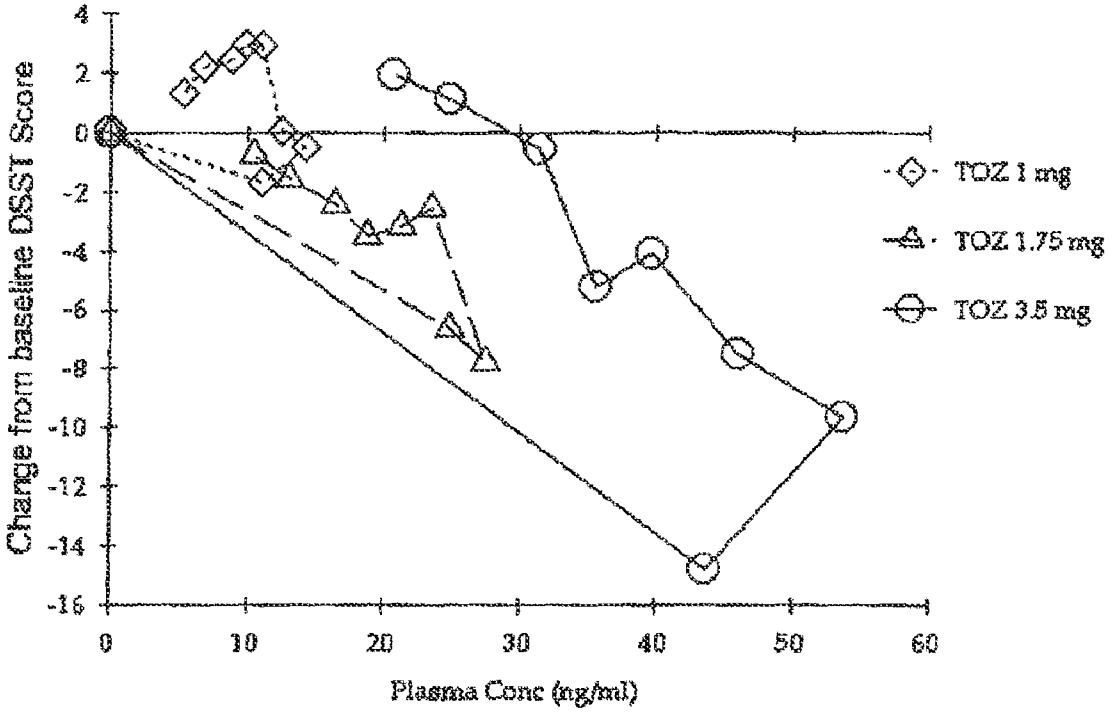
Change from baseline DSST Score
4
2
0
-2
-4
-6
-8
-10
-12
-14
-16
0
10
20
30
40
50
60
Plasma Conc (ng/ml)
TOZ 1 mg
TOZ 1.75 mg
TOZ 3.5 mg

FIG. 4

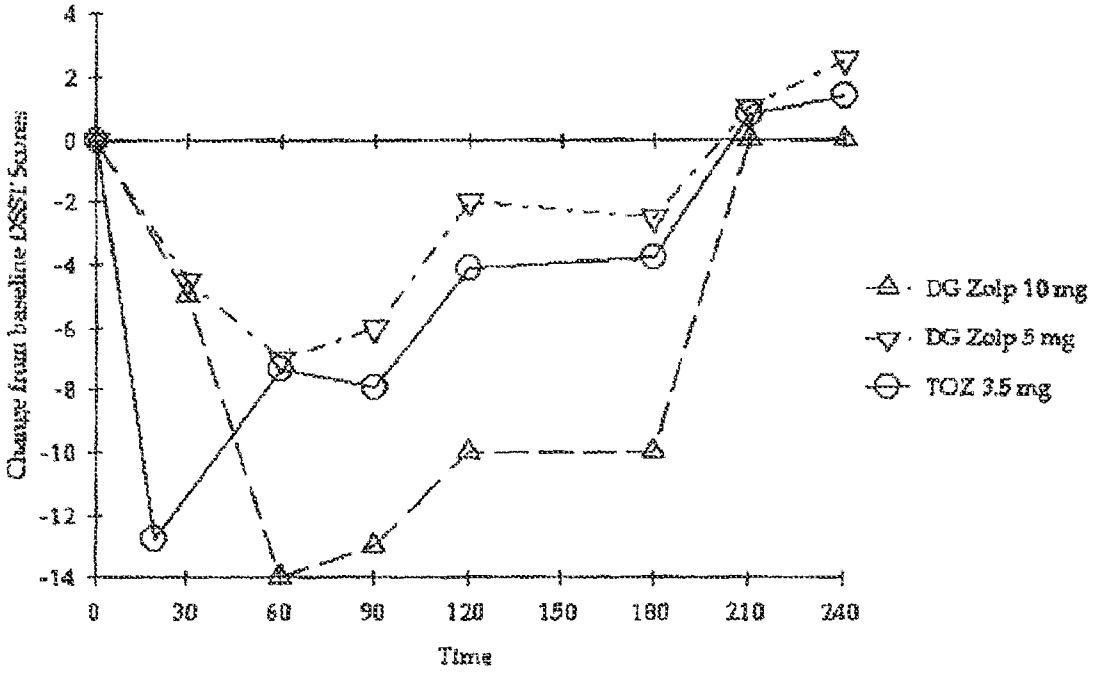
Change from baseline DSST Score
4
2
0
-2
-4
-6
-8
-10
-12
-14
0
30
60
90
120
150
180
210
240
Time
DG Zolp 10 mg
DG Zolp 5 mg
TOZ 3.5 mg

FIG. 5

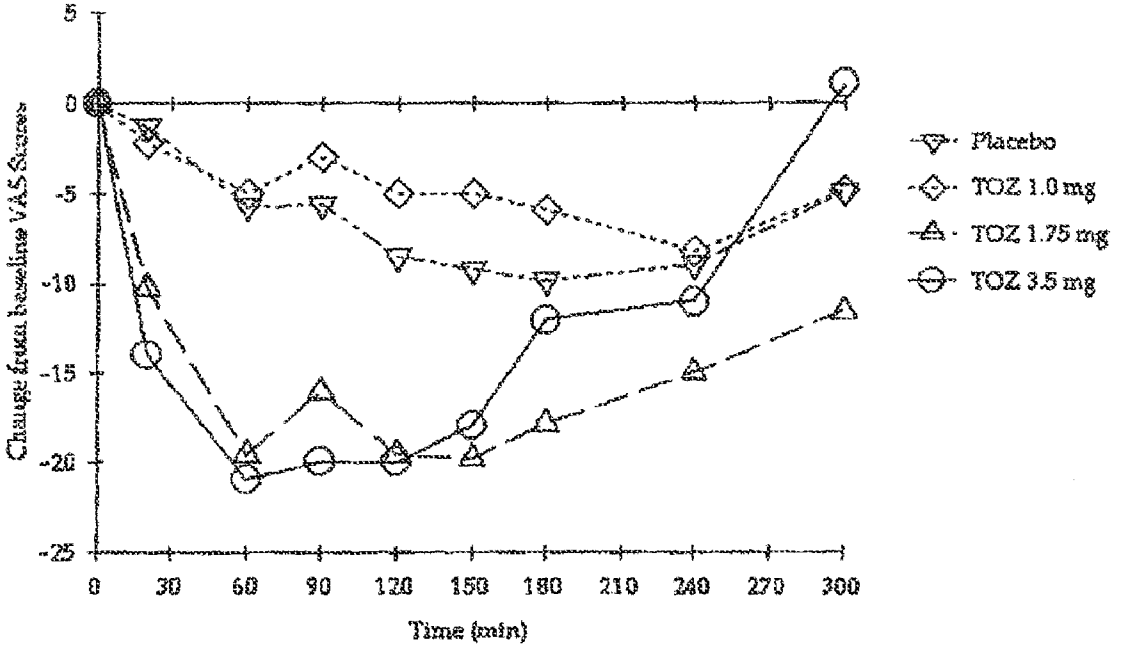
Change from baseline VAS Scores
5
0
-5
-10
-15
-20
-25
0
30
60
90
120
150
180
210
240
270
300
Time (min)
Placebo
TOZ 1.0 mg
TOZ 1.75 mg
TOZ 3.5 mg

FIG. 6

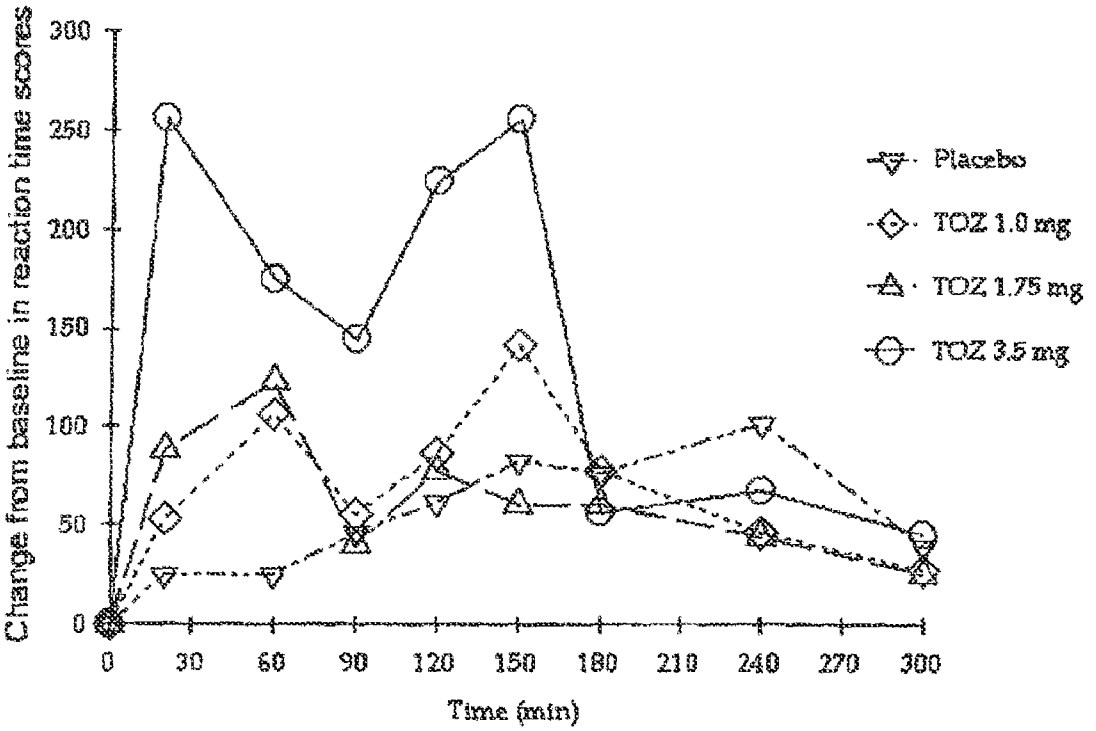
Change from baseline in reaction time scores
300
250
200
150
100
50
0
0
30
60
90
120
150
180
210
240
270
300
Time (min)
Placebo
TOZ 1.0 mg
TOZ 1.75 mg
TOZ 3.5 mg

FIG. 7

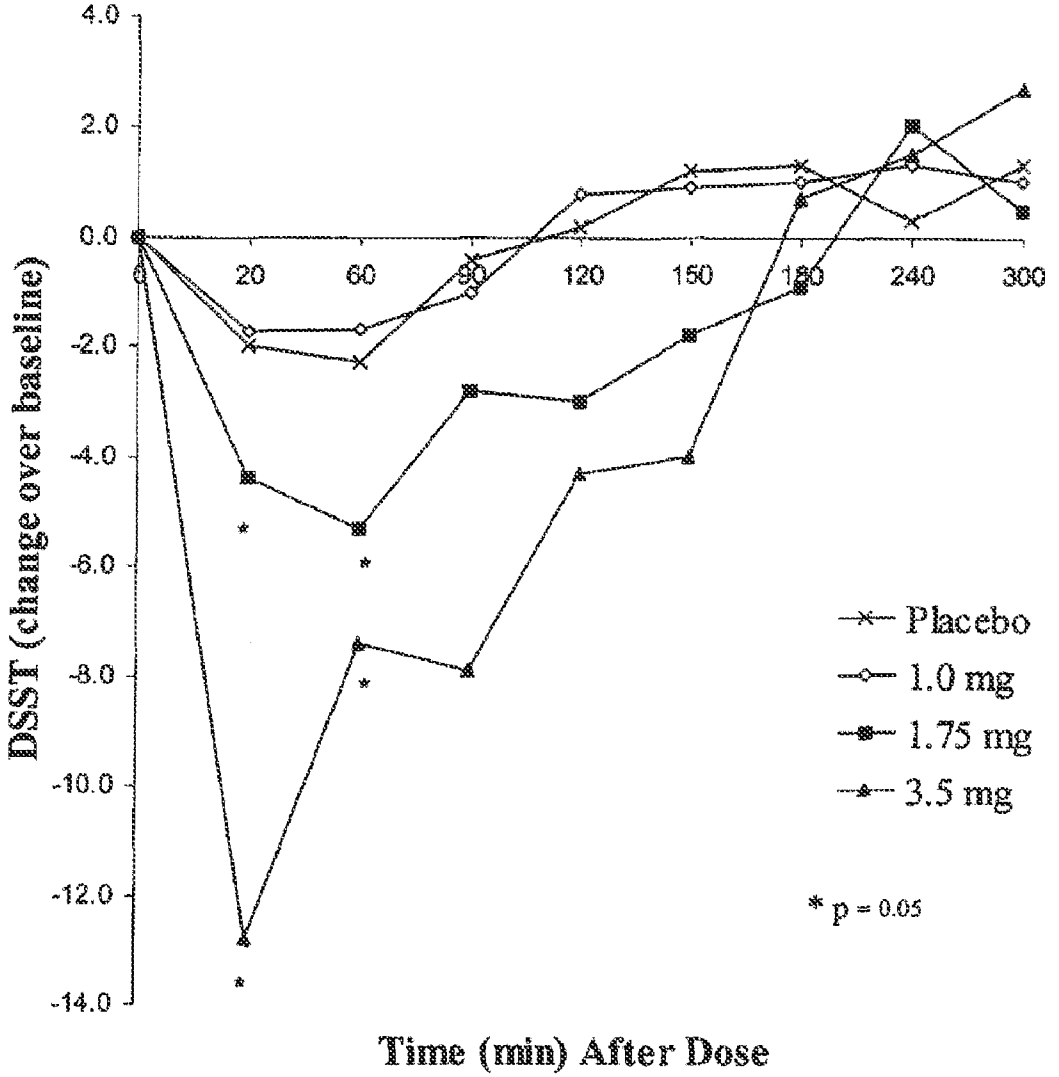
4.0
2.0
0.0
-2.0
-4.0
-6.0
-8.0
-10.0
-12.0
-14.0
0
20
60
90
120
150
180
240
300
DSST (change over baseline)
Time (min) After Dose
Placebo
1.0 mg
1.75 mg
3.5 mg
* p = 0.05

FIG. 8

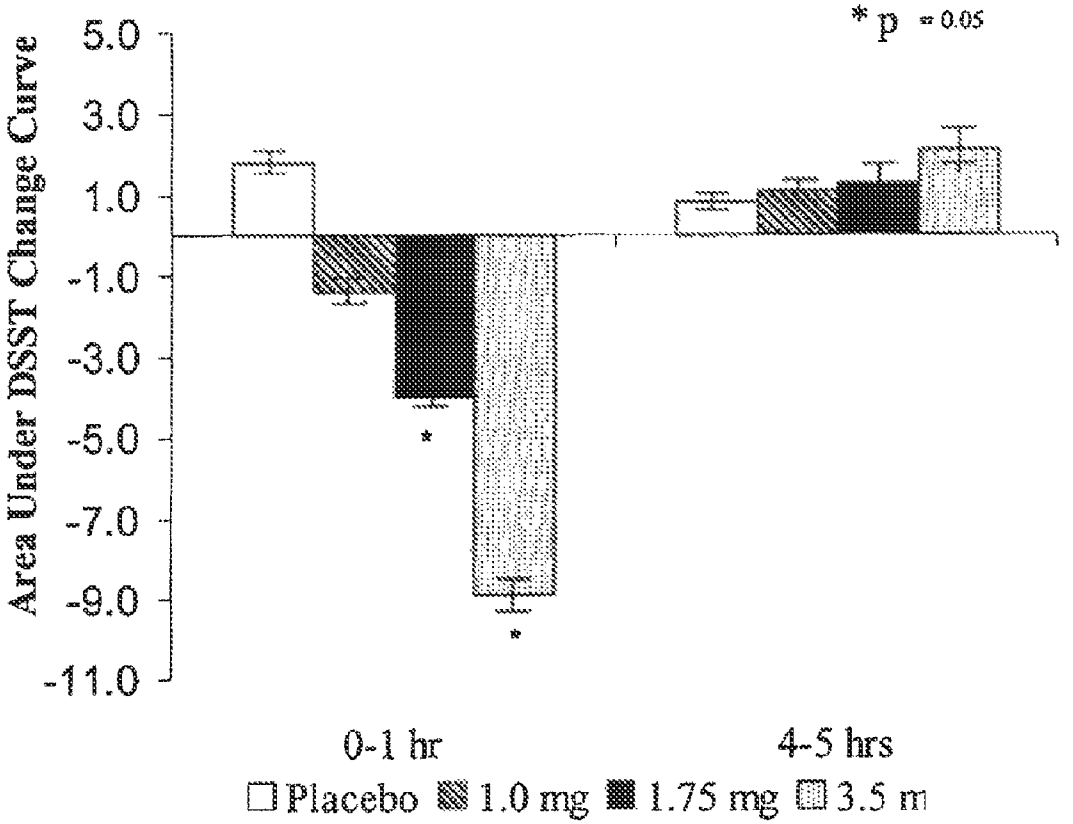
* p = 0.05
Area Under DSST Change Curve
5.0
3.0
1.0
-1.0
-3.0
-5.0
-7.0
-9.0
-11.0
*
*
0-1 hr
4-5 hrs
Placebo
1.0 mg
1.75 mg
3.5 m

FIG. 9

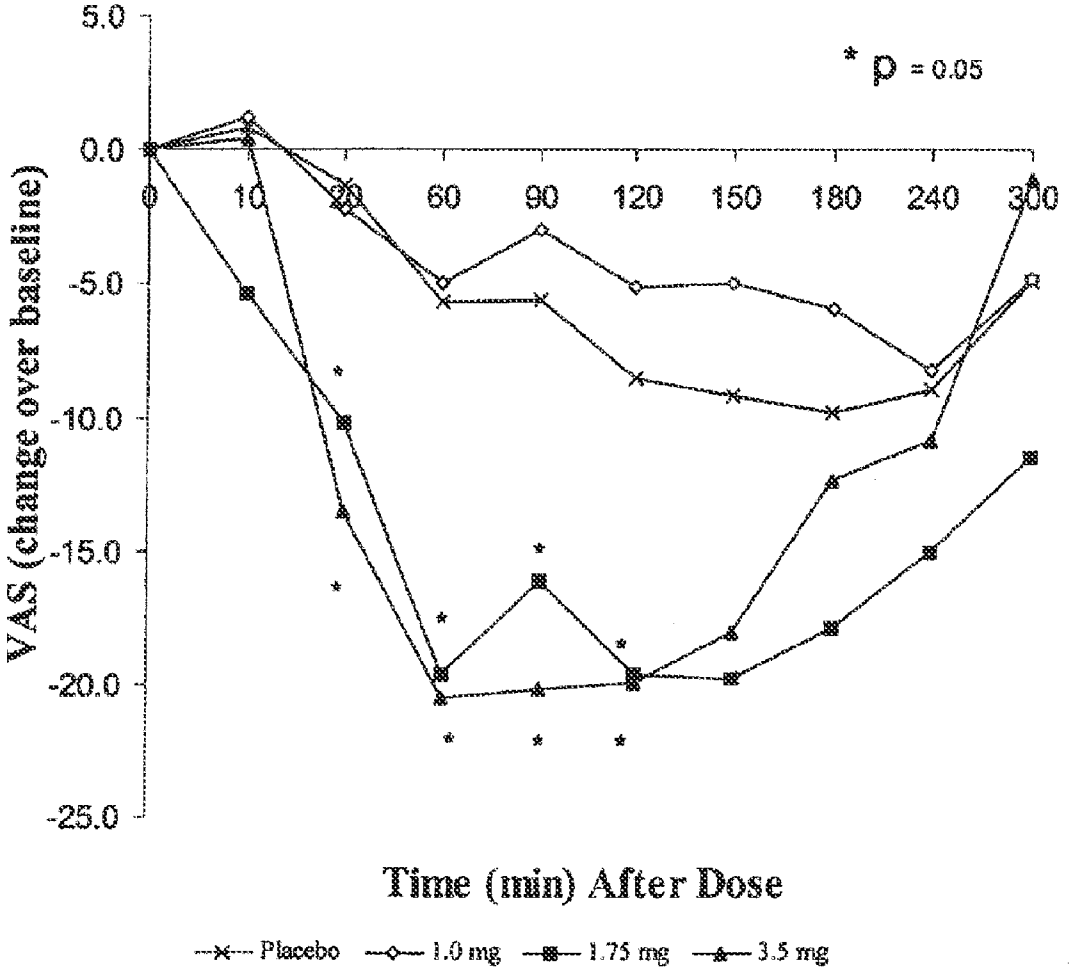
* p = 0.05
5.0
0.0
-5.0
-10.0
-15.0
-20.0
-25.0
VAS (change over baseline)
0
10
20
60
90
120
150
180
240
300
Time (min) After Dose
Placebo
1.0 mg
1.75 mg
3.5 mg

FIG. 10

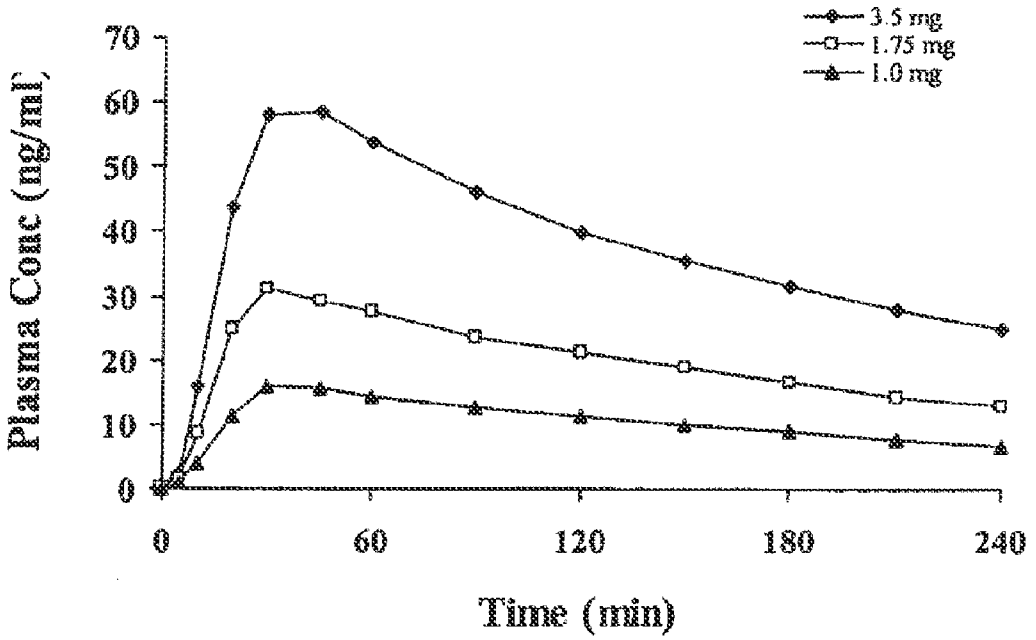
3.5 mg
1.75 mg
1.0 mg
Plasma Conc (ng/ml)
70
60
50
40
30
20
10
0
0
60
120
180
240
Time (min)

FIG. 11

COMPOSITIONS FOR TREATING INSOMNIA

CROSS-REFERENCES TO RELATED APPLICATIONS

This is a continuation of U.S. application Ser. No. 11/606,640, filed Nov. 29, 2006 now abandoned, which is a continuation-in-part of PCT/US06/20502, filed May 23, 2006, and a continuation-in-part of each of Nonprovisional application Ser. No. 11/439,873, filed May 23, 2006 now abandoned, Nonprovisional application Ser. No. 11/440,410, filed May 23, 2006, Nonprovisional application Ser. No. 11/439,874, filed May 23, 2006 now abandoned and Nonprovisional Ser. No. 11/439,884, filed May 23, 2006 now abandoned and each of which claims the benefit of U.S. Provisional Application No. 60/684,842, filed May 25, 2005, U.S. Provisional Application No. 60/741,673, filed Dec. 1, 2005, U.S. Provisional Application No. 60/788,340, filed Mar. 31, 2006, and U.S. Provisional Application No. 60/788,249, filed Mar. 31, 2006, the disclosures of which are hereby incorporated by reference in their entirety for all purposes.

BACKGROUND OF THE INVENTION

Until recently, medical literature has recognized four types of insomnia, including sleep onset insomnia (e.g., trouble falling asleep at bedtime), sleep maintenance insomnia (e.g., disturbed sleep during the night), early morning awakening, and transient insomnia (e.g., new environment, first night in hotel syndrome). However, according to the National Sleep Foundation's 2005 "Sleep in America" poll, about 20% of total respondents and about 50% of respondents reporting insomnia symptoms complained of waking up too early and having difficulty returning to sleep at least a few nights a week (results available, on the worldwide web at sleepfoundation.org). This type of insomnia includes "middle-of-the-night" insomnia, "late night" insomnia, "prolonged awakening after sleep onset" insomnia, "sleep maintenance" insomnia, and insomnia that follows after "middle-of-the-night" awakening, each of which has a component of interrupted sleep.

More particularly, patients with "middle-of-the-night" (MOTN) insomnia generally do not have problems initially falling asleep, but wake up prior to their intended wake time (during their normal sleep time), usually with about 3 to 4 hours of sleep time remaining. These patients require a treatment intervention that would reduce their wake time during their sleep time after awakening without leaving residual sedative effects in the morning. Unfortunately, currently available hypnotic medications are unsuitable for treating MOTN insomnia because they are slow to induce sleep (e.g., zaleplon) and/or require administration prior to about 7 to 9 hours in bed to avoid residual sleepiness in the morning (e.g., available dosage forms of zolpidem, eszopiclone, and zopiclone). Also, administration of most presently available hypnotics is prophylactic, resulting in unnecessary medication and overmedication of persons who require treatment for their MOTN insomnia a few nights a week.

Clearly, there remains a need for appropriate treatments for persons with MOTN insomnia. The present invention fulfills this and other needs.

BRIEF SUMMARY OF THE INVENTION

The present invention provides compositions and methods for treating MOTN insomnia with zolpidem or a salt thereof.

In one aspect, the present invention provides a solid unit dosage composition for the treatment of MOTN insomnia, the composition comprising an effective amount of zolpidem or a salt thereof, formulated for delivery of zolpidem across a subject's oral mucosa, wherein the effective amount is an amount of less than 1.30×10^{-5} moles of zolpidem, and is an amount sufficient to produce a plasma concentration between about 25 ng/ml and about 50 ng/ml within 20 minutes of administration, when evaluated in an appropriate patient population.

In another aspect, the present invention provides a solid unit dosage composition for the treatment of MOTN insomnia, the composition comprising an amount of zolpidem or a salt thereof effective to produce sleep within 30 minutes of dosing a subject, but does not produce residual sedative effects when the subject is awakened at a time about 4 hours after dosing, when the composition is evaluated in an appropriate patient population.

In yet another aspect, the present invention provides a pharmaceutical composition suitable for absorption by the oral mucosa in the treatment of MOTN insomnia, the composition comprising from about 0.5 mg to about 4.0 mg of zolpidem or a salt thereof and a pharmaceutically acceptable excipient.

In a further aspect, the present invention provides a solid pharmaceutical composition for delivery across the oral mucosa for treating insomnia comprising zolpidem in an amount less than 5 mg and a buffer.

In a related aspect, the present invention provides a solid pharmaceutical composition for delivery across the oral mucosa for treating insomnia comprising zolpidem in an amount less than 5 mg and a binary buffer.

In another related aspect, the present invention provides a solid unit dosage pharmaceutical composition comprising a dose of zolpidem hemitartrate in an amount of less than 5 mg and a binary buffer system capable of raising the pH of a subject's saliva to a pH greater than about 8.5, irrespective of the starting pH of saliva, wherein the composition is formulated for delivery of zolpidem across the subject's oral mucosa.

In an additional aspect, the present invention provides a pharmaceutical composition for treating insomnia comprising zolpidem in an amount less than 5 mg and a binary buffer.

In a related aspect, the present invention provides a pharmaceutical composition for treating insomnia comprising zolpidem in an amount less than 5 mg and a binary buffer, wherein the composition is formulated for delivery of zolpidem across the oral mucosa and the binary buffer produces a saliva pH of at least 8.5, irrespective of the starting saliva pH.

In another aspect, the present invention provides a method of treating insomnia, the method comprising:

> administering to a subject who awakens from sleep and desires to return to sleep within 30 minutes and sleep for less than 5 hours, a single unit dosage composition comprising an effective amount of zolpidem or a salt thereof, formulated for delivery of zolpidem across the subject's oral mucosa,
>
> wherein the effective amount is an amount of less than 1.30×10^{-5} moles of zolpidem, and is an amount sufficient to produce a plasma concentration between about 25 ng/ml and about 50 ng/ml within 20 minutes of administration, when evaluated in an appropriate patient population.

In a related aspect, the present invention provides a method of treating MOTN insomnia in a subject, the method comprising:

administering to the subject a pharmaceutical composition comprising zolpidem or a salt thereof in an amount of less than 1.30×10^{-5} moles of zolpidem,

wherein the administering is on an as-needed basis, and wherein delivery of zolpidem occurs across the subject's oral mucosa to produce a blood level of zolpidem in the subject between about 25 ng/ml and about 50 ng/ml within about 20 minutes of administration and less than 20 ng/ml at a time 4 hours after administration.

In yet another aspect, the present invention provides a method of treating insomnia in a subject, the method comprising:

administering to the subject a pharmaceutical composition comprising zolpidem or a salt thereof,

wherein the composition provides delivery of zolpidem across the subject's oral mucosa, wherein the subject is a subject who awakens from sleep and desires to resume sleep for less than 5 hours, and wherein the composition produces sleep within 30 minutes of dosing and the dose is such that it does not produce residual sedative effects when the subject is awakened at a time 4 hours after dosing.

In a further aspect, the present invention provides a method of treating insomnia in a subject, the method comprising:

administering a solid pharmaceutical composition comprising zolpidem in an amount less than 5 mg and a buffer, to a subject who awakens from sleep and desires to resume sleep for less than 5 hours,

wherein the solid pharmaceutical composition provides delivery of zolpidem across the subject's oral mucosa, and wherein a blood level of zolpidem is achieved in the subject of between about 25 ng/ml and about 50 ng/ml within about 20 minutes of administration.

In a related aspect, the present invention provides a method of treating insomnia, the method comprising the steps of:

providing a solid pharmaceutical composition comprising zolpidem in an amount less than 5 mg and a buffer to a patient who awakens from sleep and desires to resume sleep for less than 5 hours; and

administering the solid pharmaceutical composition to the patient for delivery of the zolpidem across the patient's oral mucosa,

wherein a blood level of zolpidem in the patient is between about 25 ng/ml and about 50 ng/ml within about 20 minutes of administration.

In an additional aspect, the present invention provides a method of treating insomnia, the method comprising:

administering a solid pharmaceutical composition comprising zolpidem in an amount less than 5 mg and a binary buffer, to a subject who awakens from sleep and desires to resume sleep for less than 5 hours,

wherein the solid pharmaceutical composition provides delivery of zolpidem across the subject's oral mucosa, wherein the solid pharmaceutical composition dissolves or disintegrates in about 2 minutes or less in the subject's mouth, and wherein the binary buffer raises the pH of saliva in the subject's mouth to a pH greater than about 9.0.

In a related aspect, the present invention provides a method of treating insomnia, the method comprising the steps of:

providing a solid pharmaceutical composition comprising zolpidem in an amount less than 5 mg and a binary buffer to a patient who awakens from sleep and desires to resume sleep for less than 5 hours; and

administering the solid pharmaceutical composition to the patient for delivery of the zolpidem across the patient's oral mucosa,

wherein the solid pharmaceutical composition dissolves or disintegrates in about 2 minutes or less in the patient's mouth, and wherein the binary buffer raises the pH of saliva in the patient's mouth to a pH greater than about 9.0.

Other objects, features, and advantages of the present invention will be apparent to one of skill in the art from the following detailed description and figures.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** shows the mean (SEM) plasma concentration time profiles of a 1.0 mg, 1.75 mg, and 3.5 mg sublingual zolpidem lozenge of the present invention.

FIG. **2** shows the predicted versus observed plasma profiles of a 1.0 mg, 1.75 mg, and 3.5 mg sublingual zolpidem lozenge of the present invention.

FIG. **3** shows the Digit Symbol Substitution Test (DSST) scores of a 1.0 mg, 1.75 mg, and 3.5 mg sublingual zolpidem lozenge of the present invention as a function of time.

FIG. **4** shows the DSST scores of a 1.0 mg, 1.75 mg, and 3.5 mg sublingual zolpidem lozenge of the present invention as a function of plasma concentration.

FIG. **5** shows a comparison of DSST scores of a 3.5 mg sublingual zolpidem lozenge of the present invention and 5 mg and 10 mg peroral (PO) Ambien® as reported in the literature.

FIG. **6** shows the Visual Analog Scale (VAS) scores of a 1.0 mg, 1.75 mg, and 3.5 mg sublingual zolpidem lozenge of the present invention.

FIG. **7** shows the change in reaction time scores as measured by a Psychomotor Vigilance Test (PVT) of a 1.0 mg, 1.75 mg, and 3.5 mg sublingual zolpidem lozenge of the present invention.

FIG. **8** shows the mean change over baseline in DSST scores of a 1.0 mg, 1.75 mg, and 3.5 mg sublingual zolpidem lozenge of the present invention.

FIG. **9** shows mean±SEM 1-hour effect areas for changes over baseline in DSST scores of a 1.0 mg, 1.75 mg, and 3.5 mg sublingual zolpidem lozenge of the present invention.

FIG. **10** shows the mean change over baseline in scores of self-rated sedation on 100-mm Visual Analog Scale (VAS) of a 1.0 mg, 1.75 mg, and 3.5 mg sublingual zolpidem lozenge of the present invention.

FIG. **11** shows plasma concentration time profiles of zolpidem following ST zolpidem administration of a 1.0 mg, 1.75 mg, and 3.5 mg ST zolpidem lozenge of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

I. General

The present invention provides compositions and methods for treating insomnia, particularly MOTN insomnia, using therapeutically effective low doses of zolpidem or a salt thereof by delivering zolpidem across the oral mucosa. The present invention is based, in part, upon the surprising discovery that low doses of zolpidem, when formulated for delivery across the oral mucosa, can induce rapid onset of sleep without residual sedative effects upon awakening 2-4 hours later. Advantages of taking a low dose amount of zolpidem (e.g., less than 5 mg or 1.30×10^{-5} moles) to counteract MOTN insomnia include rapid action to induce sleep, treat-

ment on an as-needed basis to avoid excessive and unnecessary medication, and no or minimal residual sedative effects upon awakening.

While there are various types of dosage forms, solid dosage forms for oral administration are perhaps among the most preferred by patients, and among the most prevalently used. Many of the dosage forms are medicaments formulated as tablets or capsules, which are swallowed. However, swallowed formulations have several disadvantages, including drug losses during hepatic first pass metabolism, during enzymatic degradation within the gastrointestinal tract, and during absorption to non-targeted tissues. These drug losses not only increase the variability in drug response, but also often require that the medicament be given in greater initial doses. Still further, as the drug has to pass through the gastrointestinal system in order to enter the blood stream, the time to reach a therapeutic effect may be quite long, typically around forty-five minutes or longer.

Drug delivery via the mucous membranes of the oral cavity has certain advantages, due to the properties of the oral mucosa itself. For example, the mucous membranes of the oral cavity are highly vascularized and well supplied with lymphatic drainage sites. In general, the mucous membranes of the oral cavity can be divided into five main regions: the floor of the mouth (sublingual), the cheeks (buccal), the gums (gingival), the roof of the mouth (palatal), and the lining of the lips. These regions differ from each other with respect to their anatomy, drug permeability, and physiological response to drugs. For example, in terms of permeability, sublingual is more permeable than buccal, which is more permeable than palatal. This permeability is generally based on the relative thickness and degree of keratinization of these membranes, with the sublingual mucosa being relatively thin and non-keratinized, the buccal mucosa being thicker and non-keratinized, and the palatal mucosa being intermediate in thickness, but keratinized.

Accordingly, in certain aspects, the present invention provides solid dosage forms containing low doses of zolpidem (e.g., dissolving tablets, lozenges, etc.) and methods for treating MOTN insomnia by administering such compositions to the oral mucosa to deliver and facilitate absorption of a substantial portion of the dose through the tissues of the buccal and/or sublingual cavity. In some embodiments, the solid dosage forms described herein facilitate buccal and/or sublingual absorption due to the presence of a buffer system (e.g., a bicarbonate/carbonate buffer system). Without being bound to any particular theory, the buffer system can promote the in situ conversion of a hydrophilic (i.e., charged) form of zolpidem (e.g., zolpidem hemitartrate) into its lipophilic free-base (i.e., neutral) form, which penetrates the lipid membranes in the oral mucosa more readily than the salt form. As a result, both non-elderly and elderly patients can benefit from taking a substantially lower dose of zolpidem (e.g., about 3.5 mg for non-elderly; about 1.75 mg for elderly) as compared to the lowest currently approved dose of 5 mg, thereby rapidly inducing sleep without residual sedative effects upon awakening.

It is also desirable to reduce variability in drug delivery. Surprisingly, this can be achieved by utilizing a binary buffer system capable of achieving and sustaining a final pH in the oral cavity, independent of the initial pH. Accordingly, compositions for delivering zolpidem or a salt thereof across the oral mucosa having a buffer system that produces a final pH, independent of the initial pH, and which sustains that final pH for a given period of time, are particularly desirable, and are provided herein.

II. Definitions

As used herein, the following terms have the meanings ascribed to them unless specified otherwise.

The term "sleep disorder" refers to a disruptive pattern of sleep arising from many causes including, without limitation, dysfunctional sleep mechanisms, abnormalities in physiological functions during sleep, abnormalities of the biological clock, and sleep disturbances that are induced by factors extrinsic to the sleep process. In particular, the term encompasses disorders associated with difficulties in staying asleep and/or falling asleep such as insomnia (e.g., transient, short-term, and chronic), delayed sleep phase syndrome, hypnotic-dependent sleep disorder, and stimulant-dependent sleep disorder; disorders associated with difficulties in staying awake such as sleep apnea, narcolepsy, restless leg syndrome, obstructive sleep apnea, central sleep apnea, idiopathic hypersomnia, respiratory muscle weakness-associated sleep disorder; disorders associated with difficulties in adhering to a regular sleep schedule such as sleep state misperception, shift work sleep disorder, chronic time zone change syndrome, and irregular sleep-wake syndrome; disorders associated with abnormal behaviors such as sleep terror disorder (i.e., parasomnia) and sleepwalking (i.e., somnambulism); and other disorders such as sleep bruxism, fibromyalgia, and nightmares.

The term "insomnia" refers to a sleep disorder characterized by symptoms including, without limitation, difficulty in falling asleep, difficulty in staying asleep, intermittent wakefulness, and/or waking up too early. The term also encompasses daytime symptoms such as sleepiness, anxiety, impaired concentration, impaired memory, and irritability. Types of insomnia suitable for treatment with the compositions of the present invention include, without limitation, transient, short-term, and chronic insomnia. The term "transient insomnia" refers to insomnia lasting for a few nights. The term "short-term insomnia" refers to insomnia lasting for about two to about four weeks. The term "chronic insomnia" refers to insomnia lasting for at least one month.

The phrase "prolonged awakening after sleep onset insomnia" refers to the condition wherein a subject, after falling asleep, awakens and has difficulty returning to sleep, regardless of the number of hours of time in bed remaining. "Prolonged awakening after sleep onset insomnia" includes middle-of-the-night insomnia, late night insomnia, and insomnia after early night awakening.

As used herein, the term "middle-of-the-night insomnia" or "MOTN insomnia" refers to the condition wherein a subject, after falling asleep, awakens and has difficulty returning to sleep. Typically, the subject has about 5 hours of sleep time or time in bed remaining, although in some subjects only 4 hours, 3 hours, or 2 hours of sleep time may remain. One of skill in the art will appreciate that the term middle-of-the-night refers to a middle portion of the subject's sleep time in any sleep period, rather than a specific time of a time zone, day or night. For example, a shift worker who would normally sleep from 8 am until 3 pm or 4 pm can still exhibit MOTN insomnia, when their sleep time is interrupted during normal daylight hours. MOTN insomnia can be transient, short-term, or chronic.

The term "time in bed" refers to the amount of time a subject spends in a recumbent position (e.g., lying down in bed or reclining in a chair) intending to sleep.

The term "sleep time" refers to the time that a subject spends sleeping. Sleep time can be continuous or discontinuous.

"Sleep efficiency" refers to the total sleep time a subject receives during their time in bed. Sleep efficiency is measured by the following equation:

100*(total sleep time(TST)/total time in bed).

The phrase "residual sedative effects" refers to a patient's subjective feeling of sedation upon awakening. Additionally, the term is meant to refer to a patient population as found in, for example, a clinical trial, rather than a single patient example. Residual sedative effects also can be evaluated using one or more of any of a number of tests exploring psychomotor performance, attention, information processing, and memory used by those of skill in the art including, for example, a Sleep Latency Test (SLT), a Visual Analog Test (VAT), a Digit Symbol Substitution Test (DSST), a Symbol Copying Test (SCT), a Critical Flicker Fusion threshold test (CFF), a Simple Reaction time test (visual or auditory; SRT), a Choice Reaction Time test (CRT), a Word Learning Test (WLT), a Critical Tracking Test (CTT), a Divided Attention Test (DAT), a digit or letter cancellation test, sleep staging through polysomnographic (PSG) measurements, Continuous Performance Task test (CPT), Multiple Sleep Latency Test (MSLT), a Rapid Visual Information Processing test (RVIP), a mental calculation test, a body sway test, a driving performance test, and others. Guidelines for a Sleep Latency Test are published in *Sleep* (1986) 9:519-24. The above-listed tests are described, for example, in Walsh, et al., (2000) *Clin Neuropharm* 23:17-21; Verster, et al., (2002) *J Clin Psychopharm* 22:576-583; Patat, et al, (2001) *Human Psychopharm* 16:369-392; and Hindmarch, et al., (2001) *Human Psychopharm* 16:159-167. As a result, an amount that substantially avoids or does not produce residual sedative effects is an amount that allows a subject, upon awakening following sleep time, to test acceptably in at least one of the above tests, preferably at least two or three of the above tests, and most preferably in at least four of the above tests.

Alternatively, an amount that substantially avoids or does not produce residual sedative effects can be objectively measured by determining the plasma or serum levels of zolpidem at an appropriate time point. In particular, residual sedative effects will be essentially extinguished when a subject's plasma levels of zolpidem fall below about 20 ng/ml. Again, this objective test refers to an average zolpidem plasma or serum concentration in a patient population. Because some variability between patients is expected, a number of patients may respond as having residual sedative effects even at low plasma or serum concentrations of zolpidem.

The term "therapeutically effective amount" or "effective amount" refers to the amount of zolpidem that is capable of achieving a therapeutic effect in a subject in need thereof. For example, an effective amount of zolpidem can be the amount that is capable of preventing or relieving one or more symptoms associated with MOTN insomnia. It is important to note that a plasma concentration time curve for any given drug is illustrative of four, very often overlapping, kinetic events that decide the fate of the drug inside the body after the drug is administered. The four events are absorption, distribution, metabolism, and excretion. The absorption phase dominates in the beginning, while the distribution phase dominates at peak concentration time, and metabolism and excretion phases dominate the remaining disappearing stages of the drug. The sedative-hypnotic activity profile of zolpidem can be predicted from its plasma concentration time curve (Greenblatt et al., *Clin. Pharmacol. Therap.* 64:553 (1998)). In general, plasma concentrations between about 25 ng/ml and about 50 ng/ml, which are sufficient for inducing sleep, occur during the absorption phase of the drug, but this is not necessarily the peak concentration. Once the zolpidem is absorbed and distributed, the plasma concentrations will fall off with time. When the latter phase of drug distribution, metabolism, and excretion results in concentrations of zolpidem below about 20 ng/ml, the residual sedative effects of the drug will be essentially extinguished. This level will depend, to some extent, on the patient's age, hepatic efficiency, and initial dose. Generally, for the compositions and methods described herein, the sedative-hypnotic activity does not persist once the plasma levels have dropped below about 20 ng/ml, due to concurrence of continuous depletion of drug in the body and fulfillment of sleep requirement of the sleep-wake cycle of the body.

The term "bioavailability" refers to the rate and/or extent to which a drug is absorbed or becomes available to the treatment site in the body. The MOTN efficacy of zolpidem can also be improved by improving the bioavailability or the absorption of zolpidem, e.g., at rate of about 0.1 ng/ml per minute.

The term "dissolves" or "dissolution" refers to the conversion of a portion of the solid dosage form to a solution or slurry form. The amount of the solid dosage form that dissolves over a period of time will vary depending on the components of the dosage form (e.g., the form of zolpidem used as well as the excipients used). Some solid dosage forms will completely dissolve in a patient's mouth over a time period of about 15 minutes or less. Still other solid dosage forms will completely dissolve in the mouth over a time period of about 6 minutes or less. Generally, at least about 25% by weight of the solid dosage form will dissolve within about 5 minutes of administration. Suitable methods known in the art for determining the dissolution profile of a solid dosage form include, e.g., United States Pharmacopeia (USP) dissolution tests such as USP <711> Apparatus 1 or USP <711> Apparatus 2.

The term "disintegrates" or "disintegration" refers to the breakdown of, for example, a tablet or lozenge, into small pieces accompanied by complete dissolution of a substantial portion of the solid dosage form to a liquid form. More particularly, disintegration of a solid dosage form refers to less than about 25% by weight of the solid dosage form remaining in the mouth following an appropriate time period, e.g., about 5 minutes after administration. Suitable methods known in the art for determining the disintegration profile of a solid dosage form include, e.g., the USP disintegration test.

As used herein, the phrase "substantially complete conversion of zolpidem from its ionized to its un-ionized form" refers to greater than about 50% conversion of zolpidem from its ionized form into its un-ionized form. For example, a buffer system may favor at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 99% conversion of zolpidem from its ionized form into its un-ionized form. In some embodiments, the conversion occurs within about 10 minutes following administration.

The term "variability" refers to inter-subject variability in terms of the percent of relative standard deviation (RSD) for the maximum plasma concentration (C_{max}) and the time to reach the maximum plasma concentration (T_{max}). Notably, the preferred compositions of the present invention have an RSD for C_{max} of about 33% versus about 45% for commercial oral tablets such as Ambien® tablets. Further, the compositions of the present invention have an RSD for T_{max} of about 50% or less versus about 100% for commercial oral tablets such as Ambien® tablets.

The term "subject" or "patient" refers to humans.

The term "administering" refers to administration of the compositions of the present invention to the mucous mem-

branes of the oral cavity (i.e., oral mucosa). Examples of suitable sites of administration within the oral mucosa include, without limitation, the mucous membranes of the floor of the mouth (sublingual mucosa), the cheeks (buccal mucosa), the gums (gingival mucosa), the roof of the mouth (palatal mucosa), the lining of the lips, and combinations thereof. Preferably, the compositions of the present invention are administered to the sublingual mucosa, buccal mucosa, or a combination thereof.

III. Description of the Embodiments

In one aspect, the present invention provides a solid unit dosage composition for the treatment of MOTN insomnia, the composition comprising an effective amount of zolpidem or a salt thereof, formulated for delivery of zolpidem across a subject's oral mucosa, wherein the effective amount is an amount of less than 1.30×10^{-5} moles of zolpidem, and is an amount sufficient to produce a plasma concentration between about 25 ng/ml and about 50 ng/ml within 20 minutes of administration, when evaluated in an appropriate patient population.

In one embodiment, the solid unit dosage composition provides about 50% of the maximum plasma concentration (C_{max}) of zolpidem in about 30 minutes or less, alternatively in about 20 minutes or less, or alternatively in about 10 minutes or less. In another embodiment, the solid unit dosage composition provides blood (e.g., plasma) levels of zolpidem that are less than about 20 ng/ml at a time about 2, 3, or 4 hours after dosing. The zolpidem is typically delivered across the subject's sublingual and/or buccal mucosa.

In some embodiments, the solid unit dosage composition comprises at least one pH-adjusting agent selected from the group consisting of a carbonate salt and a bicarbonate salt. In other embodiments, the solid unit dosage composition comprises a binary buffer system that raises the pH of the subject's saliva to a pH greater than about 8.5, alternatively greater than about 9.0, alternatively greater than about 9.5, alternatively greater than about 10.0, alternatively greater than about 10.5, alternatively greater than about 11.0, or alternatively between about 9.0 and about 11.0, irrespective of the starting pH of saliva. For example, the binary buffer system can comprise sodium carbonate and sodium bicarbonate. Alternatively, the binary buffer system can comprise any combination of carbonate salt and bicarbonate salt known in the art.

The solid unit dosage composition is typically in the form of a lozenge, a chewing gum, a chewable tablet, or a dissolving tablet such as a slow-dissolving tablet or a quick-dissolving tablet. Preferably, the solid unit dosage composition is a lozenge or a quick-dissolving tablet. A quick-dissolving tablet usually provides complete dissolution in the subject's mouth in less than about 0.5 minutes, alternatively in less than about 1 minute, alternatively in less than about 1.5 minutes, alternatively in less than about 2 minutes, alternatively in less than about 2.5 minutes, alternatively in less than about 3 minutes, alternatively in less than about 4 minutes, alternatively in less than about 5 minutes, or alternatively in less than about 6 minutes. A description of low dose zolpidem lozenge and tablet dosage forms is provided in Examples 1 and 3, respectively.

In another embodiment, the solid unit dosage composition contains less than about 5 mg of zolpidem hemitartrate. Preferably, the solid unit dosage composition contains from about 0.5 to about 4.75 mg of zolpidem hemitartrate, alternatively from about 1.5 to about 2.5 mg of zolpidem hemitartrate, or alternatively from about 3.0 to about 3.75 mg of zolpidem hemitartrate.

The effective amount of zolpidem is generally evaluated in an appropriate patient population (e.g., a patient population used for a clinical study) based on factors such as age, weight, the number of hours of time in bed remaining, and/or the ability of a subject to metabolize zolpidem. Accordingly, effective amounts of zolpidem for delivery across the oral mucosa may be different for selected patient populations. For example, the effective amount of zolpidem in an elderly patient population (i.e., subjects 65 years of age and older) is usually from about 1.5 mg to about 2.5 mg of zolpidem, alternatively about 1.75 mg, alternatively about 2.0 mg, or alternatively about 2.5 mg. Similarly, the effective amount of zolpidem in a population of subjects with a diminished capacity to metabolize zolpidem can be from about 1.5 mg to about 2.5 mg of zolpidem, alternatively about 1.75 mg, alternatively about 2.0 mg, or alternatively about 2.5 mg. The effective amount of zolpidem in a non-elderly patient population (i.e., subjects younger than 65 years of age) is usually from about 3.0 mg to about 3.75 mg zolpidem, alternatively about 3.25 mg, alternatively about 3.5 mg, or alternatively about 3.75 mg. The effective amount of zolpidem in subjects who have awakened but still have about 4 or 5 hours of time in bed remaining can be from about 2 mg to about 5 mg of zolpidem. A lower amount of zolpidem (e.g., from about 0.5 mg to about 2.5 mg, alternatively about 0.5 mg, alternatively about 1.0 mg, alternatively about 1.5 mg, alternatively about 2.0 mg, or alternatively about 2.5 mg) can be administered to subjects who have awakened but still have about 2 to 4 hours of time in bed remaining.

Any method known in the art can be used to determine the plasma concentration of zolpidem in a subject. As a non-limiting example, the plasma from a blood sample collected from the subject can be assayed for zolpidem levels using high pressure liquid chromatography (HPLC) followed by tandem mass spectrometry (MS) or fluorescence detection. Chromatographic methods for measuring plasma levels of zolpidem are described in, for example, Ascalone et al., *J. Chromatogr.,* 581:237-250 (1992); Tracqui et al., *J. Chromatogr.,* 616:95-103 (1993); Durol et al., *J. Anal. Toxicol.,* 215:388-392 (1997); Ptacek et al., *J. Chromatogr. B Biomed. Sci. Appl.,* 694:409-413 (1997); and Ring et al., *J. Pharm. Biomed. Anal.,* 22:495-504 (2000).

In another aspect, the present invention provides a solid unit dosage composition for the treatment of MOTN insomnia, the composition comprising an amount of zolpidem or a salt thereof effective to produce sleep within 30 minutes of dosing a subject, but does not produce residual sedative effects when the subject is awakened at a time about 4 hours after dosing, when the composition is evaluated in an appropriate patient population.

In some embodiments, the solid unit dosage composition further comprises at least one pH-adjusting agent. Examples of pH-adjusting agents include, but are not limited to, carbonate salts, bicarbonate salts, and mixtures thereof. In other embodiments, the solid unit dosage composition comprises a binary buffer system. As a non-limiting example, the binary buffer system can comprise a carbonate salt (e.g., sodium carbonate) and a bicarbonate salt (e.g., sodium bicarbonate). In a preferred embodiment, the solid unit dosage composition is in a dosage form suitable for delivery of zolpidem across the subject's oral mucosa (e.g., buccal and/or sublingual delivery), wherein the binary buffer system raises the pH of the subject's saliva to a pH greater than about 8.5, alternatively greater than about 9.0, alternatively greater than about 9.5, alternatively greater than about 10.0, alternatively greater

than about 10.5, alternatively greater than about 11.0, or alternatively between about 9.0 and about 11.0, irrespective of the starting pH of saliva.

In certain embodiments, the solid unit dosage composition produces polysomnography stage 1 sleep at the onset of sleep. Polysomnography stage 1 sleep typically refers to a non-REM stage of sleep where a polysomnogram shows about a 50% reduction in activity from wakefulness. The eyes are usually closed during polysomnography stage 1 sleep, but if aroused from it, a subject may feel as if he or she has not slept. Polysomnography stage 1 sleep may last for about 5 to about 10 minutes.

In another embodiment, the solid unit dosage composition contains less than about 5 mg of zolpidem hemitartrate. Preferably, the solid unit dosage composition contains from about 0.5 to about 4.75 mg of zolpidem hemitartrate, alternatively from about 1.5 to about 2.5 mg of zolpidem hemitartrate, or alternatively from about 3.0 to about 3.75 mg of zolpidem hemitartrate.

The solid unit dosage composition is typically in the form of a lozenge, a tablet (e.g. chewable tablet, slow-dissolving tablet, quick-dissolving tablet), or a chewing gum. Preferably, the composition is a lozenge or a quick-dissolving tablet. In some embodiments, the solid unit dosage composition provides buccal and/or sublingual dissolution in about 5 minutes or less (e.g., about 4, 3, 2, 1, or 0.5 minutes or less) following administration.

In yet another aspect, the present invention provides a pharmaceutical composition suitable for absorption by the oral mucosa (e.g., buccal and/or sublingual absorption) in the treatment of MOTN insomnia, the composition comprising from about 0.5 mg to about 4.0 mg of zolpidem or a salt thereof and a pharmaceutically acceptable excipient.

In some embodiments, the pharmaceutical composition comprises from about 0.5 to about 4.0 mg of zolpidem hemitartrate. Generally, the pharmaceutical composition can comprise about 1.0 mg, alternatively about 1.75 mg, alternatively about 2.5 mg, alternatively about 3.0 mg, or alternatively about 3.5 mg, of zolpidem or a salt thereof such as zolpidem hemitartrate. In other embodiments, the pharmaceutical composition further comprises a binary buffer system. For example, the binary buffer system can comprise a carbonate such as sodium carbonate and a bicarbonate such as sodium bicarbonate. The carbonate and bicarbonate are usually present in a carbonate:bicarbonate ratio of from about 1:1.0 to about 1:1.4 by weight, or alternatively from about 1:1.0 to about 1:1.2 by weight. Preferably, the binary buffer system raises the pH of the subject's saliva to a pH greater than about 8.5, alternatively greater than about 9.0, alternatively greater than about 9.5, alternatively greater than about 10.0, alternatively greater than about 10.5, alternatively greater than about 11.0, or alternatively between about 9.0 and about 11.0, irrespective of the starting pH of saliva.

In certain embodiments, the pharmaceutical composition is a solid unit dosage form such as a lozenge or tablet (e.g., chewable tablet, slow-dissolving tablet, quick-dissolving tablet). In another embodiment, the pharmaceutical composition provides complete buccal and/or sublingual dissolution in about 5 minutes or less (e.g., about 4, 3, 2, 1, or 0.5 minutes or less) following administration.

In a further aspect, the present invention provides a solid pharmaceutical composition for delivery across the oral mucosa for treating insomnia comprising zolpidem in an amount less than 5 mg and a buffer.

Generally, the buffer comprises a carbonate buffer, a bicarbonate buffer, or a mixture thereof. In certain instances, the buffer is a binary buffer comprising, e.g., a carbonate buffer and a bicarbonate buffer.

In some embodiments, the amount of zolpidem is less than about 1.30×10^{-5} moles of zolpidem. In other embodiments, the amount of zolpidem is from about 0.5 to about 4.75 mg of zolpidem hemitartrate, e.g., from about 1.5 to about 2.5 mg of zolpidem hemitartrate, alternatively from about 3.0 to about 3.75 mg of zolpidem hemitartrate, alternatively from about 1.0 to about 3.75 mg of zolpidem hemitartrate, or alternatively from about 1.5 to about 3.0 mg of zolpidem hemitartrate.

The solid pharmaceutical composition is typically in a dosage form including, but not limited to, a lozenge, a chewing gum, a chewable tablet, and a dissolving tablet such as a slow-dissolving tablet or a quick-dissolving tablet. Preferably, the solid pharmaceutical composition is in the form of a lozenge or a quick-dissolving sublingual tablet. The zolpidem is typically delivered across the sublingual and/or buccal mucosa.

In a related aspect, the present invention provides a solid pharmaceutical composition for delivery across the oral mucosa for treating insomnia comprising zolpidem in an amount less than about 5 mg and a binary buffer.

In one embodiment, the amount of zolpidem is from about 0.5 to about 4.75 mg of zolpidem hemitartrate. Preferably, the amount of zolpidem is from about 1.5 to about 2.5 mg of zolpidem hemitartrate, alternatively from about 3.0 to about 3.75 mg of zolpidem hemitartrate, alternatively from about 1.0 to about 3.75 mg of zolpidem hemitartrate, or alternatively from about 1.5 to about 3.0 mg of zolpidem hemitartrate. In certain other instances, the amount of zolpidem is less than about 1.30×10^{-5} moles of zolpidem.

In some embodiments, the binary buffer comprises a carbonate buffer such as sodium carbonate and a bicarbonate buffer such as sodium bicarbonate. Preferably, the solid pharmaceutical composition is a lozenge or tablet such as a sublingual tablet.

In another related aspect, the present invention provides a solid unit dosage pharmaceutical composition comprising a dose of zolpidem hemitartrate in an amount of less than about 5 mg and a binary buffer system capable of raising the pH of a subject's saliva to a pH greater than about 8.5, alternatively greater than about 9.0, alternatively greater than about 9.5, alternatively greater than about 10.0, alternatively greater than about 10.5, alternatively greater than about 11.0, or alternatively between about 9.0 and about 11.0, irrespective of the starting pH of saliva, wherein the composition is formulated for delivery of zolpidem across the subject's oral mucosa.

In one embodiment, the solid unit dosage pharmaceutical composition contains from about 0.5 to about 4.75 mg of zolpidem hemitartrate. Preferably, the solid unit dosage pharmaceutical composition contains from about 1.5 to about 2.5 mg of zolpidem hemitartrate, alternatively from about 3.0 to about 3.75 mg of zolpidem hemitartrate, alternatively from about 1.0 to about 3.75 mg of zolpidem hemitartrate, or alternatively from about 1.5 to about 3.0 mg of zolpidem hemitartrate.

In some embodiments, the binary buffer system comprises a carbonate salt such as sodium carbonate and a bicarbonate salt such as sodium bicarbonate. In other embodiments, the binary buffer system comprises a carbonate salt and a bicarbonate salt in a carbonate:bicarbonate ratio of from about 1:1.0 to about 1:1.4 by weight, or alternatively from about 1:1.0 to about 1:1.2 by weight.

In an additional aspect, the present invention provides a pharmaceutical composition for treating insomnia comprising zolpidem in an amount less than 5 mg and a binary buffer.

The pharmaceutical composition is typically in a dosage form suitable for delivery of zolpidem across a subject's oral mucosa (e.g., buccal and/or sublingual delivery) including, but not limited to, a lozenge, a chewing gum, a chewable tablet, and a dissolving tablet such as a slow-dissolving tablet or a quick-dissolving tablet. In some embodiments, the binary buffer comprises a carbonate buffer such as sodium carbonate and a bicarbonate buffer such as sodium bicarbonate. Alternatively, the binary buffer can comprise any combination of carbonate salt and bicarbonate salt known in the art.

In a related aspect, the present invention provides a pharmaceutical composition for treating insomnia comprising zolpidem in an amount less than 5 mg and a binary buffer, wherein the composition is formulated for delivery of zolpidem across the oral mucosa (e.g., buccal and/or sublingual mucosa) and the binary buffer produces a saliva pH of at least about 8.5, alternatively at least about 9.0, alternatively at least about 9.5, alternatively at least about 10.0, alternatively at least about 10.5, alternatively at least about 11.0, or alternatively between about 9.0 and about 11.0, irrespective of the starting saliva pH.

In another aspect, the present invention provides a method of treating insomnia, the method comprising:

administering to a subject who awakens from sleep and desires to return to sleep within 30 minutes and sleep for less than 5 hours, a single unit dosage composition comprising an effective amount of zolpidem or a salt thereof, formulated for delivery of zolpidem across the subject's oral mucosa,

wherein the effective amount is an amount of less than 1.30×10^{-5} moles of zolpidem, and is an amount sufficient to produce a plasma concentration between about 25 ng/ml and about 50 ng/ml within 20 minutes of administration, when evaluated in an appropriate patient population.

In the methods of the present invention, the single unit dosage composition is typically administered pro re nata ("as needed"). Preferably, the single unit dosage composition is a lozenge or tablet (e.g., chewable tablet, slow-dissolving tablet, quick-dissolving tablet) formulated for buccal and/or sublingual delivery of zolpidem. In some embodiments, the single unit dosage composition further comprises a binary buffer system that raises the pH of the subject's saliva to a pH greater than about 8.5, alternatively greater than about 9.0, alternatively greater than about 9.5, alternatively greater than about 10.0, alternatively greater than about 10.5, alternatively greater than about 11.0, or alternatively between about 9.0 and about 11.0, irrespective of the starting pH of saliva.

In a preferred embodiment, the single unit dosage composition comprises from about 0.5 to about 4.75 mg of zolpidem hemitartrate and a binary buffer system that raises the pH of the subject's saliva to a pH greater than about 8.5, alternatively greater than about 9.0, alternatively greater than about 9.5, alternatively greater than about 10.0, alternatively greater than about 10.5, alternatively greater than about 11.0, or alternatively between about 9.0 and about 11.0, irrespective of the starting pH of saliva. In one embodiment, the binary buffer system comprises sodium carbonate and sodium bicarbonate.

In a related aspect, the present invention provides a method of treating MOTN insomnia in a subject, the method comprising:

administering to the subject a pharmaceutical composition comprising zolpidem or a salt thereof in an amount of less than 1.30×10^{-5} moles of zolpidem,

wherein the administering is on an as-needed basis, and wherein delivery of zolpidem occurs across the subject's oral mucosa to produce a blood level of zolpidem in the subject between about 25 ng/ml and about 50 ng/ml within about 20 minutes of administration and less than 20 ng/ml at a time 4 hours after administration.

In one embodiment, the pharmaceutical composition provides blood (e.g., plasma) levels of zolpidem in the subject between about 25 ng/ml and about 50 ng/ml within about 20, 30, or 40 minutes of administration and less than about 20 ng/ml at a time about 2, 3, or 4 hours after administration. In another embodiment, the pharmaceutical composition provides about 50% of the maximum plasma concentration (C_{max}) of zolpidem in about 30 minutes or less, alternatively in about 20 minutes or less, or alternatively in about 10 minutes or less, following administration. Methods for determining the blood (e.g., plasma) level of zolpidem in a subject are described above. The delivery of zolpidem typically occurs across the subject's sublingual and/or buccal mucosa.

In some embodiments, the pharmaceutical composition comprises at least one pH-adjusting agent. Examples of pH-adjusting agents include, but are not limited to, carbonate salts, bicarbonate salts, and mixtures thereof. In other embodiments, the pharmaceutical composition comprises a binary buffer system that raises the pH of the subject's saliva to a pH greater than about 8.5, alternatively greater than about 9.0, alternatively greater than about 9.5, alternatively greater than about 10.0, alternatively greater than about 10.5, alternatively greater than about 11.0, or alternatively between about 9.0 and about 11.0, irrespective of the starting pH of saliva. For example, the binary buffer system can comprise sodium carbonate and sodium bicarbonate. Alternatively, the binary buffer system can comprise any combination of carbonate salt and bicarbonate salt known in the art.

The pharmaceutical composition is typically in the form of a lozenge, a chewing gum, a chewable tablet, or a dissolving tablet such as a slow-dissolving tablet or a quick-dissolving tablet (e.g., quick-dissolving sublingual tablet). In another embodiment, the pharmaceutical composition contains less than about 5 mg of zolpidem hemitartrate. An effective amount of zolpidem to be administered on an as-needed basis according to the methods of the present invention is described above. Preferably, the pharmaceutical composition contains from about 0.5 to about 4.75 mg of zolpidem hemitartrate, alternatively from about 1.5 to about 2.5 mg of zolpidem hemitartrate, or alternatively from about 3.0 to about 3.75 mg of zolpidem hemitartrate. In certain instances, the pharmaceutical composition comprises less than a 5 mg dose of zolpidem hemitartrate and a binary buffer system consisting of a carbonate salt and a bicarbonate salt.

In yet another aspect, the present invention provides a method of treating insomnia in a subject, the method comprising:

administering to the subject a pharmaceutical composition comprising zolpidem or a salt thereof,

wherein the composition provides delivery of zolpidem across the subject's oral mucosa, wherein the subject is a subject who awakens from sleep and desires to resume sleep for less than 5 hours, and wherein the composition produces sleep within 30 minutes of dosing and the dose is such that it does not produce residual sedative effects when the subject is awakened at a time 4 hours after dosing.

In one embodiment, the pharmaceutical composition produces sleep within about 20, 30, or 40 minutes of dosing but does not produce residual sedative effects when the subject is awakened at a time about 2, 3, or 4 hours after dosing. In

certain instances, the pharmaceutical composition produces polysomnography stage 1 sleep at the onset of sleep.

In another embodiment, the pharmaceutical composition produces blood (e.g., plasma) levels of zolpidem in the subject between about 25 ng/ml and about 50 ng/ml within about 20, 30, or 40 minutes of administration and/or less than about 20 ng/ml at a time about 2, 3, or 4 hours after administration. In yet another embodiment, the pharmaceutical composition provides about 50% of the maximum plasma concentration (C_{max}) of zolpidem in about 30 minutes or less, alternatively in about 20 minutes or less, or alternatively in about 10 minutes or less, following administration. The zolpidem is typically delivered across the subject's sublingual and/or buccal mucosa.

In some embodiments, the pharmaceutical composition further comprises at least one pH-adjusting agent. In other embodiments, the pharmaceutical composition further comprises a binary buffer system that raises the pH of the subject's saliva to a pH greater than about 8.5, alternatively greater than about 9.0, alternatively greater than about 9.5, alternatively greater than about 10.0, alternatively greater than about 10.5, alternatively greater than about 11.0, or alternatively between about 9.0 and about 11.0, irrespective of the starting pH of saliva. Preferably, the pharmaceutical composition comprises zolpidem hemitartrate, e.g., in an amount of less than about 5 mg. In certain instances, the pharmaceutical composition comprises from about 0.5 to about 4.75 mg of zolpidem hemitartrate, e.g., from about 1.5 to about 2.5 mg of zolpidem hemitartrate, alternatively from about 3.0 to about 3.75 mg of zolpidem hemitartrate, alternatively from about 1.0 to about 3.75 mg of zolpidem hemitartrate, or alternatively from about 1.5 to about 3.0 mg of zolpidem hemitartrate.

In a preferred embodiment, the pharmaceutical composition comprises from about 1.5 to about 2.5 mg of zolpidem hemitartrate or from about 3.0 to about 3.75 mg of zolpidem hemitartrate and a binary buffer system consisting of sodium carbonate and sodium bicarbonate.

The pharmaceutical composition is typically in a solid unit dosage form including, but not limited to, a lozenge, a chewing gum, a chewable tablet, and a dissolving tablet such as a slow-dissolving tablet or a quick-dissolving tablet. Preferably, the pharmaceutical composition is in the form of a lozenge or a quick-dissolving sublingual tablet.

In a further aspect, the present invention provides a method of treating insomnia in a subject, the method comprising:

administering a solid pharmaceutical composition comprising zolpidem in an amount less than 5 mg and a buffer, to a subject who awakens from sleep and desires to resume sleep for less than 5 hours,

wherein the solid pharmaceutical composition provides delivery of zolpidem across the subject's oral mucosa, and wherein a blood level of zolpidem is achieved in the subject of between about 25 ng/ml and about 50 ng/ml within about 20 minutes of administration.

In a related aspect, the present invention provides a method of treating insomnia, the method comprising the steps of:

providing a solid pharmaceutical composition comprising zolpidem in an amount less than 5 mg and a buffer to a patient who awakens from sleep and desires to resume sleep for less than 5 hours; and

administering the solid pharmaceutical composition to the patient for delivery of the zolpidem across the patient's oral mucosa,

wherein a blood level of zolpidem in the patient is between about 25 ng/ml and about 50 ng/ml within about 20 minutes of administration.

In one embodiment, the solid pharmaceutical composition achieves a blood (e.g., plasma) level of zolpidem in the subject between about 25 ng/ml and about 50 ng/ml within about 20, 30, or 40 minutes of administration. In another embodiment, the solid pharmaceutical composition provides a blood level of zolpidem in the subject less than about 20 ng/ml within about 2, 3, or 4 hours of administration.

In some embodiments, the solid pharmaceutical composition dissolves or disintegrates in the subject's mouth in about 2 minutes or less (e.g., about 2, 1.5, 1, or 0.5 minutes or less). In other embodiments, the solid pharmaceutical composition dissolves or disintegrates in the subject's mouth in about 3 to about 6 minutes (e.g., about 3, 3.5, 4, 4.5, 5, 5.5, or 6 minutes). The zolpidem is typically delivered across the subject's sublingual and/or buccal mucosa.

Generally, the buffer that is present in the pharmaceutical composition raises the pH of saliva in the subject's mouth to a pH greater than about 8.5, alternatively greater than about 9.0, alternatively greater than about 9.5, alternatively greater than about 10.0, alternatively greater than about 10.5, alternatively greater than about 11.0, or alternatively between about 9.0 and about 11.0, irrespective of the starting pH of saliva. Preferably, the pH of the saliva is raised above about 9.0 for at least about 2 minutes (e.g., about 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, or more minutes). In certain instances, the buffer is a binary buffer. A non-limiting example of a suitable binary buffer includes a mixture of a carbonate buffer and a bicarbonate buffer.

In an additional aspect, the present invention provides a method of treating insomnia, the method comprising:

administering a solid pharmaceutical composition comprising zolpidem in an amount less than 5 mg and a binary buffer, to a subject who awakens from sleep and desires to resume sleep for less than 5 hours,

wherein the solid pharmaceutical composition provides delivery of zolpidem across the subject's oral mucosa, wherein the solid pharmaceutical composition dissolves or disintegrates in about 2 minutes or less in the subject's mouth, and wherein the binary buffer raises the pH of saliva in the subject's mouth to a pH greater than about 9.0.

In a related aspect, the present invention provides a method of treating insomnia, the method comprising the steps of:

providing a solid pharmaceutical composition comprising zolpidem in an amount less than 5 mg and a binary buffer to a patient who awakens from sleep and desires to resume sleep for less than 5 hours; and

administering the solid pharmaceutical composition to the patient for delivery of the zolpidem across the patient's oral mucosa,

wherein the solid pharmaceutical composition dissolves or disintegrates in about 2 minutes or less in the patient's mouth, and wherein the binary buffer raises the pH of saliva in the patient's mouth to a pH greater than about 9.0.

In one embodiment, the solid pharmaceutical composition achieves a blood (e.g., plasma) level of zolpidem in the subject between about 25 ng/ml and about 50 ng/ml within about 20, 30, or 40 minutes of administration. In another embodiment, the solid pharmaceutical composition provides a blood level of zolpidem in the subject less than about 20 ng/ml within about 2, 3, or 4 hours of administration.

In some embodiments, the pH of the saliva is raised above about 9.0 for at least about 2 minutes (e.g., 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, or more minutes). In other embodiments, the binary buffer comprises a carbonate buffer and a bicarbonate buffer. The zolpidem is typically delivered across the subject's sublingual and/or buccal mucosa.

IV. Compositions

Typically, the compositions of the present invention will contain zolpidem or a salt thereof in an amount of about 0.5 mg, about 0.8 mg, about 1.0 mg, about 1.5 mg, about 1.75 mg, about 2.0 mg, about 2.5 mg, about 3.0 mg, about 3.5 mg, about 3.75 mg, about 4.0 mg, about 4.5 mg, or about 4.75 mg per administration. However, the amount of zolpidem can be any dose amount less than about 5 mg, alternatively from about 1.5 to about 2.5 mg, or alternatively from about 3.0 to about 3.75 mg. One skilled in the art will appreciate that the amount of zolpidem can be expressed as the number of moles of zolpidem present in the composition. For example, 5 mg of zolpidem hemitartrate is equivalent to about 1.30×10^{-5} moles of zolpidem. As such, in some embodiments, the composition will contain an amount of zolpidem hemitartrate that provides less than about 1.30×10^{-5} moles of zolpidem.

Any form of zolpidem is suitable for use in the compositions described herein, e.g., a salt form of zolpidem, a free base form of zolpidem, a polymorph of zolpidem, or a mixture thereof. For example, pharmaceutically acceptable salts of zolpidem can include, without limitation, tartrate, hemitartrate, succinate, dihydrochloride, salicylate, hemisuccinate, citrate, maleate, hydrochloride, carbamate, sulfate, nitrate, and benzoate salt forms, as well as combinations thereof. In some embodiments, the zolpidem is in the form of a salt, e.g., zolpidem hemitartrate. In other embodiments, the zolpidem is in the form of a polymorph, e.g., commercially available from Plantex Ltd. (Netanya, Israel).

The compositions of the present invention may take the form of solid, semi-solid, lyophilized powder, or liquid dosage forms, such as, for example, tablets (e.g., chewable, slow-dissolving, quick-dissolving, etc.), pills, capsules, lozenges, gums, powders, solutions, suspensions, emulsions, aerosols, foams, creams, gels, lotions, or the like. Preferably, the compositions of the present invention are formulated as a tablet or a lozenge, in particular quick-dissolving tablets or lozenges, such as those described in U.S. Patent Publication No. 20050226925.

As used herein, the term "unit dosage" or "dosage form" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of therapeutic agent calculated to produce the desired onset, tolerability, and therapeutic effects, in association with one or more suitable pharmaceutical excipients such as carriers. Methods for preparing such dosage forms are known or will be apparent to those skilled in the art. For example, in some embodiments, a chewing gum dosage form of the present invention can be prepared according to the procedures set forth in U.S. Pat. No. 4,405,647. In other embodiments, a liquid spray or a solution, tincture, tablet, lozenge, or candy dosage form of the present invention can be prepared according to the procedures set forth, for example, in *Remington: The Science and Practice of Pharmacy,* 20th Ed., Lippincott, Williams & Wilkins (2003); *Pharmaceutical Dosage Forms, Volume* 1*: Tablets,* 2nd Ed., Marcel Dekker, Inc., New York, N.Y. (1989); and similar publications. The dosage form to be administered will, in any event, contain a quantity of the therapeutic agent in a therapeutically effective amount for relief of the condition being treated when administered in accordance with the teachings of the present invention.

The terms "carrier" or "excipient" refer to a typically inert substance used as a diluent or vehicle for a drug such as a therapeutic agent. The term also encompasses a typically inert substance that imparts cohesive qualities to the composition. Suitable carriers for use in the compositions of the present invention include, without limitation, a binder, a gum base, and combinations thereof. Non-limiting examples of binders include mannitol, sorbitol, xylitol, maltodextrin, lactose, dextrose, sucrose, glucose, inositol, powdered sugar, molasses, starch, cellulose, microcrystalline cellulose, polyvinylpyrrolidone, acacia gum, guar gum, tragacanth gum, alginate, extract of Irish moss, panwar gum, ghatti gum, mucilage of isapol husks, Veegum®, larch arabogalactan, gelatin, methylcellulose, ethylcellulose, carboxymethylcellulose, hydroxypropylmethylcellulose, polyoxyethylene polymers, polyacrylic acid (e.g., Carbopol), calcium silicate, calcium phosphate, dicalcium phosphate, calcium sulfate, kaolin, sodium chloride, polyethylene glycol, propylene glycol, and combinations thereof. These binders can be pre-processed to improve their flowability and taste by methods known in the art such as freeze drying (see, e.g., Fundamentals of Freeze-Drying, *Pharm. Biotechnol.,* 14:281-360 (2002); Lyophililization of Unit Dose Pharmaceutical Dosage Forms, *Drug. Dev. Ind. Pharm.,* 29:595-602 (2003)); solid-solution preparation (see, e.g., U.S. Pat. No. 6,264,987); and lubricant dusting and wet-granulation preparation with a suitable lubricating agent (see, e.g., *Remington: The Science and Practice of Pharmacy*, supra). For example, Mannogem® and Sorbogem®, sold by SPI Pharma Group (New Castle, Del.), are freeze-dried processed forms of mannitol and sorbitol, respectively. Typically, the compositions of the present invention comprise from about 25% to about 90% by weight of the binder, and preferably from about 50% to about 80%. However, one skilled in the art will appreciate that the compositions of the present invention can be made without any binders, e.g., to produce a highly friable dosage form.

Non-limiting examples of gum bases include materials selected from among the many water-insoluble and saliva-insoluble gum base materials known in the art. For example, in some instances, the gum base comprises at least one hydrophobic polymer and at least one hydrophilic polymer. Non-limiting examples of suitable hydrophobic and hydrophilic polymers for gum bases include both natural and synthetic polymers such as elastomers, rubbers, and combinations thereof. Examples of suitable natural polymers include, without limitation, substances of plant origin such as chicle, jelutong, gutta percha, crown gum, and combinations thereof. Examples of suitable synthetic polymers include elastomers such as butadiene-styrene copolymers, isobutylene and isoprene copolymers (e.g., "butyl rubber"), polyethylene, polyisobutylene, polyvinylester (e.g., polyvinyl acetate and polyvinyl acetate phthalate), and combinations thereof. In other instances, the gum base comprises a mixture of butyl rubber (i.e., isobutylene and isoprene copolymer), polyisobutylene, and optionally, polyvinylacetate (e.g., having a molecular weight of approximately 12,000). Typically, the gum base comprises from about 25% to about 75% by weight of these polymers, and preferably from about 30% to about 60%.

The compositions of the present invention can additionally include lubricating agents; wetting agents; emulsifying agents; solubilizing agents; suspending agents; preserving agents such as methyl-, ethyl-, and propyl-hydroxy-benzoates, butylated hydroxytoluene, and butylated hydroxyanisole; sweetening agents; flavoring agents; coloring agents; and disintegrating agents such as crospovidone as well as croscarmellose sodium and other cross-linked cellulose polymers.

Lubricating agents can be used to prevent adhesion of the dosage form to the surface of the dies and punches, and to reduce inter-particle friction. Lubricating agents may also facilitate ejection of the dosage form from the die cavity and improve the rate of granulation flow during processing.

Examples of suitable lubricating agents include, without limitation, magnesium stearate, calcium stearate, zinc stearate, stearic acid, sodium stearyl fumarate, simethicone, silicon dioxide, talc, hydrogenated vegetable oil, polyethylene glycol, mineral oil, and combinations thereof. The compositions of the present invention can comprise from about 0% to about 10% by weight of the lubricating agent, and preferably from about 1% to about 5%.

Sweetening agents can be used to improve the palatability of the composition by masking any unpleasant tastes it may have. Examples of suitable sweetening agents include, without limitation, compounds selected from the saccharide family such as the mono-, di-, tri-, poly-, and oligosaccharides; sugars such as sucrose, glucose (corn syrup), dextrose, invert sugar, fructose, maltodextrin, and polydextrose; saccharin and salts thereof such as sodium and calcium salts; cyclamic acid and salts thereof; dipeptide sweeteners; chlorinated sugar derivatives such as sucralose and dihydrochalcone; sugar alcohols such as sorbitol, sorbitol syrup, mannitol, xylitol, hexa-resorcinol, and the like, and combinations thereof. Hydrogenated starch hydrolysate, and the potassium, calcium, and sodium salts of 3,6-dihydro-6-methyl-1-1,2,3-oxathiazin-4-one-2,2-dioxide may also be used. Of the foregoing, sorbitol, mannitol, and xylitol, either alone or in combination, are preferred sweetening agents. The compositions of the present invention can comprise from about 0% to about 80% by weight of the sweetening agent, preferably from about 5% to about 75%, and more preferably from about 25% to about 50%.

Flavoring agents can also be used to improve the palatability of the composition. Examples of suitable flavoring agents include, without limitation, natural and/or synthetic (i.e., artificial) compounds such as peppermint, spearmint, wintergreen, cinnamon, menthol, cherry, strawberry, watermelon, grape, banana, peach, pineapple, apricot, pear, raspberry, lemon, grapefruit, orange, plum, apple, fruit punch, passion fruit, chocolate (e.g., white, milk, dark), vanilla, caramel, coffee, hazelnut, combinations thereof, and the like. Coloring agents can be used to color code the composition, for example, to indicate the type and dosage of the therapeutic agent therein. Suitable coloring agents include, without limitation, natural and/or artificial compounds such as FD & C coloring agents, natural juice concentrates, pigments such as titanium oxide, silicon dioxide, and zinc oxide, combinations thereof, and the like. The compositions of the present invention can comprise from about 0% to about 10% by weight of the flavoring and/or coloring agent, preferably from about 0.1% to about 5%, and more preferably from about 2% to about 3%.

When the dosage form is a chewing gum, the composition can comprise zolpidem or a pharmaceutically acceptable salt thereof ("therapeutic agent"), a carrier or excipient such as a gum base, a pH-adjusting agent or buffer system, and optionally a protecting agent. The chewing gum composition may further comprise lubricating agents, wetting agents, emulsifying agents, solubilizing agents; suspending agents, preserving agents, sweetening agents, flavoring agents, and coloring agents. Typically, the chewing gum composition comprises less than about 5 mg (e.g., from about 0.5 mg to about 4.75 mg, from about 1.5 mg to about 2.5 mg, from about 3.0 mg to about 3.75 mg, etc.) of zolpidem or a salt thereof. One skilled in the art understands that the foregoing amounts will vary depending upon the particular source of zolpidem utilized, the amount of zolpidem desired in the final formulation, as well as on the particular release rate of zolpidem desired. In certain instances, the buffer system of the chewing gum composition provides a final salivary pH in excess of at least about 7.8, preferably at least about 8.5, and more preferably at least about 9 (e.g., about 9-11). The chewing gum composition typically comprises from about 20% to about 95% by weight of the gum base, more typically from about 30% to about 85%, and most typically from about 50% to about 70% of the gum base.

The chewing gum composition may further comprise a protecting agent. The protecting agent coats at least part of the therapeutic agent, typically upon the mixing of the two agents. The protecting agent may be mixed with the therapeutic agent in a ratio of from about 0.1 to about 100 by weight, preferably in a ratio of from about 1 to about 50, and more preferably in a ratio of from about 1 to about 10. Without being bound to any particular theory, the protecting agent reduces the adhesion between the therapeutic agent and the gum base so that the therapeutic agent may be more easily released from the gum base. In this way, the therapeutic agent may be delivered across the mucous membranes of the oral cavity within about 5 to about 20 minutes of chewing, preferably within about 10 minutes of chewing. A variety of different protecting agents may be used. Examples of suitable protecting agents include, without limitation, calcium stearate, glycerin monostearate, glyceryl behenate, glyceryl palmitostearate, hydrogenated castor oil, hydrogenated vegetable oil type I, light mineral oil, magnesium lauryl sulfate, magnesium stearate, sodium stearyl fumarate, mineral oil, poloxamer, polyethylene gycol, sodium benzoate, sodium chloride, sodium lauryl sulfate, stearic acid, cab-o-sil, talc, zinc stearate, and combinations thereof.

The gum base may additionally include plasticizers such as softeners or emulsifiers. Such plasticizers may, for example, help reduce the viscosity of the gum base to a desirable consistency and improve its overall texture and bite. Plasticizers may also facilitate the release of the therapeutic agent upon mastication. Non-limiting examples of plasticizers include lecithin, mono- and diglycerides, lanolin, stearic acid, sodium stearate, potassium stearate, glycerol triacetate, glycerol monostearate, glycerin, and combinations thereof. The gum base typically comprises from about 0% to about 20% by weight of the plasticizer, and more typically from about 5% to about 15%.

The gum base may further comprise waxes such as beeswax and microcrystalline wax, fats or oils such as soybean and cottonseed oil, and combinations thereof. Typically, the gum base comprises from about 0% to about 25% by weight of these waxes and oils, and more typically comprises from about 15% to about 20%.

In addition, the gum base may further comprise one or more elastomeric solvents such as rosins and resins. Non-limiting examples of such solvents include methyl, glycerol, and pentaerythritol esters of rosins, modified rosins such as hydrogenated, dimerized or polymerized rosins, or combinations thereof (e.g., pentaerythritol ester of partially hydrogenated wood rosin, pentaerythritol ester of wood rosin, glycerol ester of wood rosin, glycerol ester of partially dimerized rosin, glycerol ester of polymerized rosin, glycerol ester of tall oil rosin, glycerol ester of wood rosin and partially hydrogenated wood rosin and partially hydrogenated methyl ester of rosin such as polymers of alpha-pinene or beta-pinene, terpene resins including polyterpene, and combinations thereof). Typically, the gum base comprises from about 0% to about 75% by weight of the elastomeric solvent, and more typically less than about 10%.

The gum base may further comprise a filler material to enhance the chewability of the final chewing gum composition. Fillers that are substantially non-reactive with other components of the final chewing gum formulation are pref-

erable. Examples of suitable fillers include, without limitation, calcium carbonate, magnesium silicate (i.e., talc), dicalcium phosphate, metallic mineral salts (e.g., alumina, aluminum hydroxide, and aluminum silicates), and combinations thereof. Typically, the gum base comprises from about 0% to about 30% by weight of the filler, and more typically from about 10% to about 20%.

One skilled in the art will appreciate that the gum base need not be prepared from its individual components. For example, the gum base can be purchased with the desired ingredients contained therein, and can be modified to include additional agents. Several manufacturers produce gum bases suitable for use with the described chewing gum compositions. Examples of such gum bases include, without limitation, Pharmagum™ M. S. or C(SPI Pharma Group; New Castle, Del.). In general, Pharmagum™ comprises a mixture of gum base, sweetening agent, plasticizer, and sugar.

In certain instances, the chewing gum composition includes a therapeutic agent centerfill. A centerfill may be particularly suitable when immediate release of the therapeutic agent is preferred. In addition, encapsulating the therapeutic agent in a centerfill may help to mask any undesirable taste that the therapeutic agent may have. In these instances, the gum base surrounds, at least in part, a centerfill. The centerfill comprises at least one therapeutic agent, and may be a liquid or semi-liquid material. The centerfill material can be a synthetic polymer, a semi-synthetic polymer, low-fat, or fat-free and contain one or more sweetening agents, flavoring agents, coloring agents, and/or scenting agents. Preferably, the centerfill includes a buffer system as described herein. Methods for preparing a centerfill chewing gum are described, for example, in U.S. Pat. No. 3,806,290.

The chewing gum compositions can have any desired shape, size, and texture. For example, the chewing gum can have the shape of a stick, tab, gumball, and the like. Similarly, the chewing gum can be any desirable color. For example, the chewing gum can be any shade of red, blue, green, orange, yellow, violet, indigo, and mixtures thereof, and can be color coded to indicate the type and dosage of the therapeutic agent therein. The chewing gum can be individually wrapped or grouped together in pieces for packaging by methods well known in the art.

When the dosage form is a tablet such as a dissolving tablet or chewable tablet, the composition can comprise zolpidem or a pharmaceutically acceptable salt thereof, a carrier or excipient such as a binder, and a pH-adjusting agent or buffer system. The tablet composition may further comprise protecting agents, lubricating agents, wetting agents, emulsifying agents, solubilizing agents; suspending agents, preserving agents, sweetening agents, flavoring agents, coloring agents, and disintegrating agents. Typically, the tablet compositions of the present invention comprise less than about 5 mg (e.g., from about 0.5 mg to about 4.75 mg, from about 1.5 mg to about 2.5 mg, from about 3.0 mg to about 3.75 mg, etc.) of zolpidem or a salt thereof. One skilled in the art understands that the foregoing amounts will vary depending upon the particular source of zolpidem utilized, the amount of zolpidem desired in the final formulation, as well as on the particular release rate of zolpidem desired. In certain instances, the buffer system of the tablet compositions provide a final salivary pH in excess of at least about 7.8, preferably at least about 8.5, and more preferably at least about 9 (e.g., about 9-11).

In certain embodiments, the tablet is a dissolving tablet such as a slow-dissolving or quick-dissolving tablet that is dissolved by a subject's saliva, without the need for chewing. For example, a dissolving tablet placed on the subject's tongue can be used for buccal delivery of the therapeutic agent. Alternatively, a dissolving tablet placed underneath the subject's tongue can be used for sublingual delivery of the therapeutic agent. This type of dosage form may be particularly desirable for pediatric and geriatric patients, since small children and aged individuals often have difficulty chewing certain items. Typically, the dissolving tablet is formulated to dissolve within about 1 to about 15 minutes, preferably within about 2 to about 10 minutes, e.g., within about 2, 3, 4, 5, 6, 7, 8, 9, or 10 minutes, following administration. One skilled in the art will understand that quick-dissolving tablets dissolve faster than slow-dissolving tablets, which are typically dissolved gradually rather than rapidly by a subject's saliva. In a preferred embodiment, the slow-dissolving or quick-dissolving tablet delivers the therapeutic agent across the sublingual mucosa.

In certain other embodiments, the tablet is a chewable tablet that is chewed by a subject and formulated to dissolve either rapidly or gradually. For example, a chewable tablet placed on the subject's tongue can be used for buccal delivery of the therapeutic agent. During chewing, the chewable tablet can be moved around within the mouth and can sometimes be parked between the gums and the cheeks or underneath the tongue. As a result, at least a portion of the therapeutic agent contained within a chewable tablet may also be delivered sublingually (i.e., across the sublingual mucosa). Typically, the chewable tablet is formulated to dissolve within about 1 to about 15 minutes, preferably within about 2 to about 10 minutes, e.g., within about 2, 3, 4, 5, 6, 7, 8, 9, or 10 minutes, following administration.

As described above, the dissolving and chewable tablets of the present invention are typically formulated to dissolve within about 1 to about 15 minutes following administration. However, while these time frames are amenable to maximum exposure of the therapeutic agent to the oral mucosa (e.g., to the sublingual and/or buccal mucosa), they are not always amenable to user compliance (e.g., users may swallow too frequently and, therefore, hinder maximal transmucosal absorption). Consequently, in certain instances, it may be desirable to strike a balance between patient compliance and maximum exposure time of the therapeutic agent to the oral mucosa. This can be accomplished, for example, by reducing the tablet size (e.g., from about 700-800 mg to about 200-300 mg or about 100-350 mg) without reducing the concentration or amount per unit dose of the buffer system or the therapeutic agent. In addition, subtle changes to the tablet formulation such as, for example, replacing one flavoring agent for another (e.g., chocolate for spearmint) or replacing one binder or sweetening agent for another (e.g., lactose for mannitol or sorbitol) may be used to reduce salivation.

The carrier or excipient present in the tablets of the present invention is typically a binder that is useful in keeping the tablet in a semi-solid state, and may be a solid or a liquid, and may for example be a high-melting point fat or waxy material. Materials suitable as binders are discussed in detail above and may be used alone or in combination in the tablet compositions of the present invention. In addition, binders such as mannitol, sorbitol, lactose, sucrose, and inositol can impart properties to the tablet that permit or enhance its disintegration in the mouth.

The tablet composition may also comprise one or more elastomeric solvents such as rosins and resins. Non-limiting examples of such solvents are discussed in detail above and may be used alone or in combination in the tablet compositions of the present invention. In addition, the tablet composition may further comprise waxes such as beeswax and microcrystalline wax, fats or oils such as soybean and cotton-

seed oil, and combinations thereof. Moreover, the tablet composition may additionally include plasticizers such as softeners or emulsifiers. Such plasticizers may, for example, help reduce the viscosity of the salivary solution of the dissolved tablet to a desirable consistency and improve its overall texture and bite and help facilitate the release of the therapeutic agent. Non-limiting examples of such plasticizers are discussed in detail above and may be used alone or in combination in the tablet compositions of the present invention.

In certain instances, the tablet composition includes a therapeutic agent centerfill, e.g., as described above. In certain other instances, the tablet composition of the present invention is multilayered. In this way, the dissolving or chewable tablet can be designed to provide more than one therapeutic agent. For example, with a bi-layered tablet, the first layer can contain zolpidem or a salt thereof and the second layer can contain the same or different hypnotic agent or a non-hypnotic agent. Typically, the first layer comprises the dissolving or chewable portion of the tablet, and the second (i.e., subsequent) layer is coated by the first layer. This type of formulation may be particularly suitable when immediate release of zolpidem, followed by gastrointestinal absorption of a second therapeutic agent, is desirable. Gastrointestinal absorption of the second therapeutic agent may be desirable, for example, in order to mitigate co-morbid symptoms or to sustain the therapeutic benefit of zolpidem in the dissolving or the chewable portion of the tablet. Alternatively, the second layer is present as a layer lateral to the first layer. The second layer typically comprises at least one therapeutic agent, and can also comprise one or more sweetening agents, flavoring agents, coloring agents, and scenting agents as described above. In some instances, the second layer further includes a buffer system as described herein.

In still other instances, the combination of zolpidem or a salt thereof with other hypnotic agents and/or non-hypnotic agents need not take the form of a multilayered tablet, but instead comprises a single homogenous tablet layer. This type of formulation may also be used in the case where gastrointestinal absorption of at least one therapeutic agent is desirable. In this case, the relative extent of ionization of the two or more therapeutic agents determines how they are to be absorbed. For example, those therapeutic agents that are un-ionized are absorbed through the oral mucosa, while the ionized agents are swallowed for gastrointestinal absorption.

The tablet compositions can have any desired shape, size, and texture. For example, the tablet can have the shape of a stick, tab, pellet, sphere, and the like. Similarly, the tablet can be any desirable color. For example, the tablet can be any shade of red, blue, green, orange, yellow, violet, indigo, and mixtures thereof, and can be color coded to indicate the type and dosage of the therapeutic agent therein. The tablets can be individually wrapped or grouped together in pieces for packaging by methods well known in the art.

When the dosage form is a lozenge or candy, the composition can comprise zolpidem or a pharmaceutically acceptable salt thereof, a carrier or excipient such as a binder, and a pH-adjusting agent or buffer system. The lozenge or candy composition may further comprise protecting agents, lubricating agents, wetting agents, emulsifying agents, solubilizing agents; suspending agents, preserving agents, sweetening agents, flavoring agents, coloring agents, and disintegrating agents. A general discussion of lozenges and candies is provided, e.g., in *Pharmaceutical Dosage Forms, Volume 1: Tablets,* 2nd Ed., Marcel Dekker, Inc., New York, N.Y., pages 75-418 (1989). Typically, the lozenge compositions of the present invention comprise less than about 5 mg (e.g., from about 0.5 mg to about 4.75 mg, from about 1.5 mg to about 2.5 mg, from about 3.0 mg to about 3.75 mg, etc.) of zolpidem or a salt thereof. One skilled in the art understands that the foregoing amounts will vary depending upon the particular source of zolpidem utilized, the amount of zolpidem desired in the final formulation, as well as on the particular release rate of zolpidem desired. In certain instances, the buffer system of the lozenge compositions provides a final salivary pH in excess of at least about 7.8, preferably at least about 8.5, and more preferably at least about 9 (e.g., about 9-11).

In certain embodiments, the lozenge or candy is dissolved by a subject's saliva, without the need for chewing. For example, a lozenge placed on the subject's tongue can be used for buccal delivery of the therapeutic agent. Alternatively, a lozenge placed underneath the subject's tongue can be used for sublingual delivery of the therapeutic agent. This type of dosage form may be particularly desirable for pediatric and geriatric patients, since small children and aged individuals often have difficulty chewing certain items. Typically, the lozenge is formulated to dissolve within about 1 to about 15 minutes, preferably within about 2 to about 10 minutes, e.g., within about 2, 3, 4, 5, 6, 7, 8, 9, or 10 minutes, following administration. In a preferred embodiment, the lozenge or candy delivers the therapeutic agent across the sublingual mucosa.

As described above, the lozenges the present invention are typically formulated to dissolve within about 1 to about 15 minutes following administration. However, while these time frames are amenable to maximum exposure of the therapeutic agent to the oral mucosa (e.g., to the sublingual and/or buccal mucosa), they are not always amenable to user compliance (e.g., users may swallow too frequently and, therefore, hinder maximal transmucosal absorption). Consequently, in certain instances, it may be desirable to strike a balance between patient compliance and maximum exposure time of the therapeutic agent to the oral mucosa. This can be accomplished, for example, by reducing the lozenge size (e.g., from about 700-800 mg to about 200-300 mg or about 100-350 mg) without reducing the concentration or amount per unit dose of the buffer system or the therapeutic agent. In addition, subtle changes to the lozenge formulation such as, for example, replacing one flavoring agent for another (e.g., chocolate for spearmint) or replacing one binder or sweetening agent for another (e.g., lactose for mannitol or sorbitol) may be used to reduce salivation.

The carrier or excipient present in the lozenges of the present invention is typically a binder that is useful in keeping the lozenge in a semi-solid state, and may be a solid or a liquid, and may for example be a high-melting point fat or waxy material. Materials suitable as binders are discussed in detail above and may be used alone or in combination in the lozenge compositions of the present invention. In addition, binders such as mannitol, sorbitol, lactose, sucrose, and inositol can impart properties to the lozenge that permit or enhance its disintegration in the mouth.

The lozenge composition may also comprise one or more elastomeric solvents such as rosins and resins. Non-limiting examples of such solvents are discussed in detail above and may be used alone or in combination in the lozenge compositions of the present invention. In addition, the lozenge composition may further comprise waxes such as beeswax and microcrystalline wax, fats, or oils such as soybean and cottonseed oil, and combinations thereof. Moreover, the lozenge composition may additionally include plasticizers such as softeners or emulsifiers. Such plasticizers may, for example, help reduce the viscosity of the salivary solution of the dissolved lozenge to a desirable consistency and improve its overall texture and bite and help facilitate the release of the

therapeutic agent. Non-limiting examples of such plasticizers are discussed in detail above and may be used alone or in combination in the lozenge compositions of the present invention.

In other embodiments, the lozenge composition includes a therapeutic agent centerfill, is multilayered, or comprises a single homogenous lozenge layer, e.g., as described in detail above.

The lozenge compositions can have any desired shape, size, and texture. For example, the lozenge can have the shape of a stick, tab, pellet, sphere, and the like. Similarly, the lozenge can be any desirable color. For example, the lozenge can be any shade of red, blue, green, orange, yellow, violet, indigo, and mixtures thereof, and can be color coded to indicate the type and dosage of the therapeutic agent therein. The lozenges can be individually wrapped or grouped together in pieces for packaging by methods well known in the art.

In a preferred embodiment, the average particle size of the drug in the compositions described herein is about 20 microns, as compared to a typical average drug particle size of from about 75 to about 100 microns. In another preferred embodiment, the average particle size of the drug in the compositions described herein is less than or equal to the average particle size of the carrier ingredients (e.g., gum base, binders, etc.).

Typically, the pharmaceutical compositions are suitable for buccal or sublingual administration of zolpidem in the low doses provided herein. Compositions suitable for buccal or sublingual administration of zolpidem are those that provide absorption in the buccal cavity of at least about 10%, 20%, or 25% of the dosage of zolpidem in the composition. This amount is generally at least twice the amount of buccal absorption that could be expected for a tablet designed to be swallowed for absorption of the active agent in the gut. Additionally, the time to C_{max} is reduced for such compositions relative to tablets or capsules designed to deliver zolpidem in the gut. The compositions suitable for buccal or sublingual administration of zolpidem in low doses, as noted above, are sufficient to reduce the time to C_{max}, enhancing the early effect of zolpidem and increase plasma levels of zolpidem, generally two-fold or more during the first 20 minutes after administration, relative to tablets or capsules designed for delivery in the gut (e.g., to be swallowed immediately upon ingestion).

Typically, the compositions that are suitable for the treatment of MOTH insomnia following buccal or sublingual administration have a unique and discriminatory dissolution profile. Such a dissolution method relies on modified USP method II dissolution procedure and where the pH of the dissolution medium is 6.8, which approximates the pH of the saliva. The method is considered to be a modification as the volume of the medium is reduced to 500 ml from 1 liter and the paddle speed for dissolution is reduced to 15 rpm from a typical speed of 50 or more rpm. This method is sufficiently sensitive to discriminate a 2 to 3 minute dissolution tablet from a tablet that would normally take 5 minutes or more to dissolve in the mouth. Typically, a tablet that would dissolve in the mouth in 3 minutes or less would dissolve more rapidly under experimental conditions of modified USP method II than a tablet that takes 5 or more minutes to dissolve in the mouth (see, Tables 1-2 below)

TABLE 1

Exploratory dissolution profiles of 3 and 5 minute dissolution of zolpidem lozenges using the modified USP dissolution method II.

	Lozenge			
	"3 minute" dissolution prototype		"5 minute" dissolution prototype	
Time (min)	Dissolution	RSD*	Dissolution	RSD*
5	28.60%	5%	8.70%	12.00%
10	58.40%	10%	20.00%	11.30%
20	79.00%	20%	38.30%	11.40%

(500 ml of pH 6.8 phosphate buffer at a 37° C. and paddle speed of 15 rpm).

*Relative standard deviation

TABLE 2

Illustrative dissolution profiles of 1, 3.5, and 10 mg "3 minute" zolpidem lozenges using the modified USP dissolution method II. (500 ml of pH 6.8 phosphate buffer at a 37° C. and paddle speed of 15 rpm).

	Lozenge					
	1 mg "3 minute" dissolution prototype		3.5 mg "3 minute" dissolution prototype		10 mg "3 minute" dissolution prototype	
Time (min)	Dissolution	RSD	Dissolution	RSD	Dissolution	RSD
5	28.70%	11.60%	42.40%	11.14%	28.60%	19.90%
10	46.90%	9.30%	70.20%	6.53%	58.40%	10.40%
15	60.40%	6.70%	81.00%	7.23%		
20	70.50%	5.20%	84.30%	7.14%	79.00%	5.10%

In some embodiments, the compositions of the present invention provide complete buccal and/or sublingual dissolution in about 2 minutes or less following administration. The quick-dissolving tablets of the present invention usually provide complete buccal and/or sublingual dissolution in less than about 0.5 minutes, alternatively in less than about 1 minute, alternatively in less than about 1.5 minutes, alternatively in less than about 2 minutes, alternatively in less than about 2.5 minutes, alternatively in less than about 3 minutes, alternatively in less than about 4 minutes, alternatively in less than about 5 minutes, or alternatively in less than about 6 minutes.

Generally, the compositions described herein comprise a binary or a ternary buffer system, the system comprised of at least one proton donating (acidic) component and at least one proton accepting (basic) component. The components of the buffer system are selected such that their buffering capacity is greatest (the buffer system has a pK value) at a pH of from

about 7.2-11.0, usually at a pH of about, for example, 7.2, 7.6, 7.8, 8.0, 8.3, 8.5, 8.8, 9.0, 9.4, 9.5, 9.6, 9.7, or 9.8.

In preferred embodiments, the binary buffer system raises the pH of saliva to a pH greater than about 7.2, 7.6, 7.8, 8.0, 8.3, 8.5, or 8.8, irrespective of the starting pH of saliva. In other embodiments, the binary buffer system raises the pH of saliva to a pH greater than about 9.0, 9.4, 9.5, 9.6, 9.7, or 9.8 (e.g., about 9-11), irrespective of the starting pH of saliva.

Preferably, the buffer system comprises a carbonate and a bicarbonate component. For example, the carbonate salt can be selected from the group consisting of sodium carbonate, potassium carbonate, calcium carbonate, ammonium carbonate, and magnesium carbonate. The bicarbonate salt can be selected from the group consisting of sodium bicarbonate, potassium bicarbonate, calcium bicarbonate, ammonium bicarbonate, and magnesium bicarbonate. In a preferred embodiment, the binary buffer system comprises sodium carbonate and sodium bicarbonate. In another preferred embodiment, the sodium bicarbonate is dessicant-coated sodium bicarbonate. The cations of the carbonate and the bicarbonate components can be the same or different.

The concentration of each buffer system component is tailored such that the final salivary pH is achieved and sustained for a period of time, e.g., for at least about 2 minutes, at least about 5 minutes, at least about 10 minutes, at least about 20 minutes, or at least about 60 minutes. This typically involves a sensory and safety trial and error type of procedure of adding various amounts of each buffer system component and then measuring the final pH over time. In this way, selection of an appropriate weight ratio for each buffer system component can be determined. For example, the weight ratio of carbonate salt to bicarbonate salt can be from about 1:10 to about 10:1, preferably from about 1:5 to about 5:1, more preferably from about 1:4 to about 4:1 or from about 1:3 to about 3:1, and still more preferably from about 1:2 to about 2:1.

In some embodiments, the amount of bicarbonate salt is greater than or equal to the amount of carbonate salt, and the weight ratio of carbonate salt to bicarbonate salt is from about 1:1 to about 1:10, preferably from about 1:1 to about 1:5, and more preferably from about 1:1 to about 1:2, e.g., 1:1, 1:1.1, 1:1.2, 1:1.3, 1:1.4, 1:1.5, 1:1.6, 1:1.7, 1:1.8, 1:1.9, or 1:2. Alternatively, the amount of bicarbonate salt is less than or equal to the amount of carbonate salt, and the weight ratio of carbonate salt to bicarbonate salt is from about 1:1 to about 10:1, preferably from about 1:1 to about 5:1, and more preferably from about 1:1 to about 2:1, e.g., 1:1, 1.1:1, 1.2:1, 1.3:1, 1.4:1, 1.5:1, 1.6:1, 1.7:1, 1.8:1, 1.9:1, or 2:1. In some embodiments, the combined amount of carbonate salt and bicarbonate salt is greater than or equal to the amount of zolpidem, and the weight ratio of carbonate salt and bicarbonate salt to zolpidem is preferably from about 1:1 to about 10:1, e.g., 1:1, 2:1, 3:1, 4:1, 5:1, 6:1, 7:1, 8:1, 9:1, or 10:1. Alternatively, the combined amount of carbonate salt and bicarbonate salt is less than or equal to the amount of zolpidem, and the weight ratio of carbonate salt and bicarbonate salt to zolpidem is preferably from about 1:1 to about 1:10, e.g., 1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, 1:8, 1:9, or 1:10.

In some embodiments, the binary buffer system used in compositions described above comprises a carbonate salt such as sodium carbonate and a bicarbonate salt such as sodium bicarbonate, wherein the carbonate salt and the bicarbonate salt are in a carbonate:bicarbonate ratio of from about 1:1.0 to about 1:1.4 by weight, or alternatively from about 1:1.0 to about 1:1.2 by weight.

In other embodiments, the bicarbonate can be used by itself to promote selective absorption of zolpidem.

Other buffer systems are suitable for use in the compositions of the present invention, in addition to or in substitution of a carbonate and bicarbonate buffer system. For example, in an alternative embodiment, the buffer system comprises a carbonate salt or a bicarbonate salt and a second buffering agent such as a metal oxide, a citrate salt, a phosphate salt, a borate salt, an ascorbate salt, an acetate salt, and alkaline starch. In another alternative embodiment, the buffer system comprises a metal oxide and a citrate, phosphate, or borate salt. In yet another alternative embodiment, the buffer system is a ternary buffer system comprising a carbonate salt, a bicarbonate salt, and a third buffering agent such as a metal oxide, a citrate salt, a phosphate salt, a borate salt, an ascorbate salt, an acetate salt, and alkaline starch. In still yet another alternative embodiment, the buffer system comprises a carbonate salt or a bicarbonate salt and two or more buffering agents selected from the group consisting of a metal oxide, a citrate salt, a phosphate salt, and a borate salt.

In still other embodiments, the pharmaceutical compositions comprise a carrier comprising at least one binder and at least one disintegrating agent in such relative proportion to provide a buccal or sublingual dissolution time of about 5 minutes or less, preferably about 2 minutes or less, following administration. Preferably, the ratio of the binder to the disintegrating agent is from about 0.1 to about 10.0, more preferably from about 0.1 to about 1.0, and most preferably from about 0.26 to about 0.79. However, one skilled in the art will appreciate that the compositions of the present invention can be made without any binders, e.g., to produce a highly friable dosage form.

In a preferred embodiment, the zolpidem is delivered across an oral mucosa selected from the group consisting of the sublingual mucosa, the buccal mucosa, and a combination thereof. In a particularly preferred embodiment, the composition is administered sublingually so that the zolpidem is delivered across the sublingual mucosa.

In preferred embodiments of the present invention, the zolpidem is formulated in a binary buffer system comprising sodium carbonate and sodium bicarbonate. Such compositions are preferably formulated in the form of a lozenge, candy, or dissolving tablet (e.g., slow-dissolving tablet or quick-dissolving tablet) for sublingual administration. As a result, upon sublingual administration, zolpidem is delivered across the sublingual mucosa. In another preferred embodiment, the sodium bicarbonate is dessicant-coated sodium bicarbonate. A combined weight percent of sodium carbonate and sodium bicarbonate that is greater than or equal to the weight percent of zolpidem is also preferred.

In some embodiments, the composition comprises from about 0.4, 0.45, or 0.5 to about 1.5, 1.6, 1.7, or 1.8 weight percent zolpidem; from about 6.0 to about 10.0 weight percent sodium carbonate; and from about 9.0 to about 13.0 weight percent dessicant-coated sodium bicarbonate. In a preferred embodiment, the composition comprises about 0.47, 0.8, or 1.7 weight percent zolpidem; about 8.0 weight percent sodium carbonate; and about 11.0 weight percent dessicant-coated sodium bicarbonate. Such compositions are preferably in the form of a lozenge or candy with a mass of from about 100 to about 300 mg, e.g., about 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, and 300 mg. The lozenges or tablets dissolve in a subject's mouth at a very rapid rate, e.g., within about 2-3 minutes following administration.

In certain other instances, the composition comprises from about 0.4, 0.45, or 0.5 to about 1.5, 1.6, 1.7, or 1.8 weight percent zolpidem; from about 5.0 to about 9.0 weight percent sodium carbonate; and from about 7.0 to about 11.0 weight

percent sodium bicarbonate. In a preferred embodiment, the composition comprises about 0.47, 0.8, or 1.7 weight percent zolpidem; about 7.0 weight percent sodium carbonate; and about 9.0 weight percent sodium bicarbonate. Such compositions are preferably in the form of a dissolving tablet such as a slow-dissolving tablet or a quick-dissolving tablet of from about 100 to about 300 mg, e.g., about 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, and 300 mg. The quick-dissolving tablets dissolve in a subject's mouth at a rapid rate, e.g., within about 5 minutes following administration, and the slow-dissolving tablets dissolve in a subject's mouth at a slower rate, e.g., within about 10 minutes following administration.

V. Methods

In carrying out the methods of the present invention for treating MOTN insomnia, the appropriate effective dosage to be administered to a subject can be evaluated in an appropriate patient population that has been selected based on factors such as age, weight, the number of hours of time in bed remaining, and/or the ability of a subject to metabolize zolpidem. For example, a dose of about 2 mg to about 5 mg can be administered to a subject who awakens and still has about 4 or 5 hours of time in bed remaining. Similarly, a dose of about 3 mg to about 5 mg can be administered to non-elderly subjects (i.e., subjects younger than 65 years of age) with a normal capacity to metabolize zolpidem. If the subject awakens with about 2-4 hours of time in bed remaining, a dose of about 0.5 mg to about 2.5 mg can be administered. Likewise, subjects with a diminished capacity to metabolize zolpidem (i.e., subjects 65 years of age and older) can be administered a portion of a dose that would be administered to a subject with a normal capacity to metabolize zolpidem, for example, a half-tablet dose. One of skill in the art will appreciate that there can be some variability in the dose provided to some individuals. For example, hepatically-impaired individuals may use a very low dose such as that typically provided for an elderly patient.

Typically, an effective amount of zolpidem is administered to a subject with MOTN insomnia on an as needed basis, i.e., pro re nata. That is, the individual had previously fallen asleep, and the sleep time has been interrupted with at least about 2, 3, 4, or 5 hours of time in bed remaining. Generally, in practicing the present methods, zolpidem is not administered prophylactically, or before initial onset of sleep.

Typically, the methods are carried out by administering a composition of the present invention as described above. Compositions of particular interest for treating MOTN insomnia contain less than about 5 mg of zolpidem or a salt thereof. In certain embodiments, the zolpidem can be administered in a quick-dissolving tablet or lozenge. Efficient delivery of zolpidem can be achieved using a formulation with a binary or a ternary buffer system, for example with carbonate and bicarbonate components, as described above.

Administration of the compositions of the present invention is preferably carried out via any of the accepted modes of administration to the mucous membranes of the oral cavity. Examples of suitable sites of administration within the oral mucosa include, without limitation, the mucous membranes of the floor of the mouth (sublingual mucosa), the cheeks (buccal mucosa), the gums (gingival mucosa), the roof of the mouth (palatal mucosa), the lining of the lips, and combinations thereof. These regions differ from each other with respect to their anatomy, drug permeability, and physiological response to drugs. Preferably, the compositions of the present invention are administered to the sublingual mucosa, buccal mucosa, or a combination thereof.

The oral mucosa, possessing a rich blood supply and suitable drug permeability, is an especially attractive route of administration for systemic drug delivery. Furthermore, delivery of a therapeutic agent across the oral mucosa bypasses hepatic first pass metabolism, avoids enzymatic degradation within the gastrointestinal tract, and provides a more suitable enzymatic flora for drug absorption. As used herein, the term "sublingual delivery" refers to the administration of a therapeutic agent across the mucous membranes lining the floor of the mouth and/or the ventral tongue. The term "buccal delivery" as used herein refers to the administration of a therapeutic agent across the mucous membranes lining the cheeks.

VI. Examples

The following examples are offered to illustrate, but not to limit, the claimed invention.

Example 1

Low Dose Zolpidem Lozenge Compositions

Individuals suffering from middle-of-the-night insomnia are given lozenges containing 0 mg, 1.0 mg, 1.75 mg, or 3.5 mg zolpidem for sublingual delivery that are prepared according to the formulations set forth in Table 3.

TABLE 3

Low dose zolpidem lozenge formulations.

	Quantity (mg/lozenge) Strength				
Component	Placebo	1.0 mg	1.75 mg	1.75 mg	3.5 mg
Zolpidem hemitartrate	0	1.0	1.75	1.75	3.5
Pharmaburst ™ B2	143	142	69.75	141.25	139.5
Consisting of:					
mannitol					
sorbitol					
crospovidone					
silicon dioxide					
Croscarmellose sodium	10	10	5	10	10
Sodium carbonate	17	17	8.5	17	17
Sodium bicarbonate	23	23	11.5	23	23
Natural and artificial spearmint FONA# 913.004	6.5	6.5	3.25	6.5	6.5
Silicon dioxide	5.5	5.5	2.75	5.5	5.5
Sucralose	1.5	1.5	0.75	1.5	1.5
Magnesium stearate	3.5	3.5	1.75	3.5	3.5
Total lozenge weight	210	210	105	210	210

The individuals self-administer one lozenge of the above formulations when their sleep is interrupted and they have at least 2 hours of sleep time remaining. Upon awakening, the individuals provide a subjective self-assessment of any residual sedative effects and are given the following psychomotor and memory tests to evaluate any residual sedative effects: a digit symbol substitution test (DSST), a choice reaction time (CRT), a symbol copy test (SCT), and a Buschke Memory Recall Test.

Individuals receiving a placebo lozenge are generally unable to fall back asleep and therefore do not feel refreshed in the morning. Individuals receiving lozenges containing 1.0 mg, 1.75 mg, or 3.5 mg zolpidem fall asleep within about 20 minutes after self-administration of the lozenge and exhibit no or minimal residual sedative effects as evaluated by subjective self-assessment and any of the above-referenced psychomotor and memory tests.

Example 2

Pharmacokinetic and Pharmacodynamic Investigation of Low Dose Zolpidem Lozenge Compositions

This example provides an evaluation of the daytime dose-dependent pharmacokinetic and pharmacodynamic effects of the 1.0 mg, 1.75 mg, and 3.5 mg zolpidem lozenges described in Table 3 above.

Summary

Currently, no medications are available to be used on a pro re nata basis for patients who have middle-of-the-night (MOTN) awakening and who have difficulty falling back asleep. An appropriate therapeutic agent for such insomnia would enable patients to return to sleep rapidly and wake up in the morning without residual effects. This study illustrates, inter alia, that the low dose zolpidem lozenges of the present invention enhance rapid systemic delivery of zolpidem without affecting other pharmacokinetic parameters.

Healthy adults (n=24; mean age=37.6 yrs) participated in this double-blind, placebo-controlled, 4-way crossover study of 2 consecutive days of morning dosing with placebo, or 1 mg, 1.75 mg, or 3.5 mg of the low dose zolpidem lozenges of the present invention. After morning dosing, on Day 1 of each period, pharmacodynamic endpoints (DSST, PVT, VAS-sedation, SCT, and Buschke) were evaluated at pre-dose and at 20 minutes 1, 1.5, 2, 3, 4, and 5 hours post-dose. On Day 2, repeated blood samples for pharmacokinetic assessment were drawn over 12 hours.

Baseline DSST scores (±SE) were 57.6±2.9, 58.0±3.1, 58.4±2.3, and 56.9±2.7 for the placebo, 1 mg, 1.75 mg, and 3.5 mg zolpidem lozenge, respectively. Significant reductions in DSST scores were found for the 1.75 mg and 3.5 mg zolpidem lozenges at the beginning of 20 minutes (−6.6; p=0.0132 and −14.8; p<0.001, respectively) and lasted for 1.5 hours post-dose. Other endpoints showed results similar to DSST. Mean T_{max} was 36.0, 37.9, and 37.9 minutes for the 1 mg, 1.75 mg, and 3.5 mg zolpidem lozenge, respectively. Zolpidem C_{max} and AUC were dose-proportional. The 1.75 mg and 3.5 mg zolpidem lozenges reached sedation plasma levels (about 20 ng/ml) within 15 minutes, and these levels were maintained for 15 to 240 minutes.

Low dose zolpidem lozenges provide daytime sedative properties at a dose and a T_{max} of less than half of the approved dose of peroral (PO) zolpidem (10 mg) in adults. This study demonstrates that the low dose sublingual zolpidem lozenges of the present invention can be used to shorten sleep onset upon MOTN administration.

Methods

Design

This was a four-way crossover, placebo controlled, randomized double blind study with healthy male (n=13) and female (n=11) volunteers. Each treatment period consisted of two single-dose consecutive treatment days, and each treatment was separated by a wash-out period of 6 days or more. During each period, lozenges were administered approximately 24 hours apart, and the subjects received the same treatment on each day. During each period, in order to avoid any learning or drug-anticipatory response, the pharmacodynamic effects were measured on Day 1 and blood samples drawn on Day 2 for pharmacokinetic assessment.

Pharmacodynamic assessment consisted of measurements of sedation, memory, and vigilance tests. The sedative effects were quantified by a decrease in post- to pre-dose scores on a Digit Symbol Substitution Test (DSST) and self-rated assessment sedation on a Visual Analog Scale (VAS). Vigilance was assessed by an increase in post- to pre-dose scores by measurement of reaction time and number of lapses in reaction to digital stimuli using a computerized Psychomotor Vigilance Test (PVT). A decrease in post- to pre-dose scores on a Buschke Word Recall Test (Buschke) was used for memory effects. Additionally, a Symbol Copy Test (SCT) was used for measurement of simple cognitive function. The results were statistically analyzed using SAS, ANOVA procedures and significance was assessed using Dunnett's test for comparison.

Serial blood samples were drawn for up to 12 hours at pre-dose, 5, 10, 20, 30, and 45 minutes and 1, 2, 2.5, 3, 3.5, 4, 5, 6, 8, and 12 hours. Non-compartmental pharmacokinetic parameters were estimated using the WinNonlin program (Pharsight Corp.; Palo Alto, Calif.). The parameters estimated were AUC and partial AUC, C_{max}, t_{max}, and $t_{1/2}$.

Additionally, the plasma levels of the 1.0 mg, 1.75 mg, and 3.5 mg zolpidem lozenges were predicted following single compartment first order input and output modeling of data for a 10 mg zolpidem lozenge using the following equation:

$$Ct=D*K01/V/(K01-K10)*\mathrm{EXP}(-K10*T)-\mathrm{EXP}(-K01*T),$$

wherein Ct=predicted plasma concentration, D=dose, V=apparent volume of distribution, T=time, K01=absorption rate constant, and K10=the elimination rate constant. The values for V, K01 and K10 were obtained by fitting the plasma data from the 10 mg zolpidem lozenge (i.e., 3 minute dissolution lozenge swallowed every 2 minutes) to the above equation. Unless otherwise indicated, standard deviation is the variance parameter associated with the mean values.

Results

Pharmacokinetics

Zolpidem was rapidly absorbed and eliminated from each of the three low dose sublingual lozenge formulations. The plasma profiles of the three lozenge formulations are shown in FIG. **1**, and summary statistics of the pharmacokinetic parameters are described in Table 4. Overall, the t_{max} and C_{max} of the three lozenge formulations were significantly shorter and higher, respectively, than the values either predicted by modeling of the 10 mg data (see, FIG. **2**) or reported in the literature.

TABLE 4

Mean (% CV) bioavailability parameters of the low dose zolpidem lozenges.

Dose mg	C_{max} ng/ml	t_{max} min	AUC 0-12 hr ng · hr/ml	AUC 0-20 mn ng · hr/ml	Mean Bioavailability Rate (ng/ml per min)
1.0	17.77 (33%)	36 (30%)	65.31 (40%)	1.53 (42%)	0.49
1.75	32.17 (32%)	37.9 (42%)	119.54 (40%)	3.20 (42%)	0.85
3.5	64.14 (33%)	37.9 (40%)	229.42(40%)	5.80 (41%)	1.69

In particular, this pharmacokinetic study provided the following key observations:

1. The 3.5 mg lozenge produced a C_{max} of about 64 ng/ml in about 38 minutes with an AUC0-12 hr of about 229 ng.hr/ml. The mean value AUC0-20 min was 5.80 ng.hr/ml.
2. The values of the C_{max} and t_{max} for the 1.75 mg lozenge were about 32 ng/ml and 38 minutes, respectively. The values of AUC0-12 hr and AUC0-20 min were 119.54 and 3.20 ng.hr/ml, respectively.
3. The values of the C_{max} and t_{max} for the 1 mg lozenge were about 18 ng/ml and 36 minutes, respectively. The values of AUC0-12 hr and AUC0-20 min were 65.31 and 1.53 ng.hr/ml, respectively.
4. The observed values of C_{max} of all three lozenge formulations were significantly higher than the values predicted by pharmacokinetic modeling of the 10 mg data.
5. The pharmacokinetics of the three lozenge formulations were proportional to the dose.

Pharmacodynamics

Digit Symbol Substitution Test (DSST): The DSST is an objective measure of sedation. As shown in FIG. **3**, the 1.75 mg and 3.5 mg zolpidem lozenges produced peak changes in DSST scores within 20 to 60 minutes of administration, and scores returned to baseline within 3 to 4 hours of administration. These scores were significantly different from baseline for up to about 90 minutes. The DSST scores for the 1 mg zolpidem lozenge were statistically similar to that of the placebo.

FIG. **4** shows that the relationship between plasma levels of the zolpidem lozenges and the DSST response is characterized by an anti-clockwise hysteresis loop, which is typical for sedative-hypnotics. This indicates that the rapid pharmacodynamic effects are primarily due to the rapid bioavailability of the zolpidem present in the lozenges and not due to any changes in the receptor pharmacology of the drug.

One of the most surprising findings from the DSST scores for the 3.5 mg zolpidem lozenge is that the sedative response is more rapid than the values reported in the literature for 5 mg and 10 mg peroral (PO) Ambien® (see, Greenblatt et al., *Clin. Pharmacol. Therap.*, 64:553-561 (1998); Greenblatt et al., *Clin. Pharmacol. Therap.*, 64:661-671 (1998)). In particular, FIG. **5** shows that the 3.5 mg zolpidem lozenge was capable of inducing sleep more rapidly than both 5 mg and 10 mg PO Ambien®, but did not cause the excessive sedation associated with 10 mg PO Ambien®.

Self-rated assessment of sedation on VAS: Unlike DSST, the subjective sedative effects of the 1.75 mg and 3.5 mg zolpidem lozenges were similar (FIG. **6**). The Visual Analog Scale (VAS) scores for these low zolpidem doses were statistically different than placebo for up to 2 hours.

Vigilance changes as measured by PVT: The 3.5 mg zolpidem lozenge also impaired vigilance, as measured by reaction times using a Psychomotor Vigilance Test (PVT). FIG. **7** shows that the reaction time scores for the 3.5 mg zolpidem lozenge were statistically different for up to about 90 minutes.

Memory impairment (Buschke): Except for the significant effect seen at 20 minutes with the 3.5 mg zolpidem lozenge, the drug effects were comparable to that of the placebo.

Simple motor task impairment (SCT): The effects of the three lozenge formulations were comparable to that of the placebo.

Conclusions

1. Surprisingly, the zolpidem blood levels established at several time points up to 30 minutes after dosing with the 3.5 mg zolpidem lozenge exceeded those reported in the literature for PO Ambien® doses up to and including 10 mg. In fact, the 3.5 mg zolpidem lozenge was superior to 10 mg PO Ambien® (which contains nearly 3 times the dose of zolpidem) because it provided a significantly greater sedative effect at 30 minutes as measured by DSST testing.
2. The C_{max} (maximum plasma concentration) of zolpidem from the low dose zolpidem lozenges was about 30% higher than the values predicted by pharmacokinetic modeling of data for a 10 mg zolpidem lozenge. The mean C_{max} (64 ng/ml) of the 3.5 mg zolpidem lozenge was in the same range as the values reported for 5 mg PO Ambien®. Further, both 1.75 mg and 3.5 mg zolpidem lozenges produced plasma levels at 30 minutes or earlier that have been reported in the literature to produce sedative effects.
3. The low dose zolpidem lozenges achieved maximum plasma concentrations in about 36 to 38 minutes. A t_{max} of about 35 minutes was significantly earlier than the t_{max} of 1 to 1.5 hours typically reported for 5 mg and 10 mg PO zolpidem (Ambien®), eszopiclone (Lunesta™), zaleplon (Sonata®), and remelteon (Rozerem™).
4. The pharmacodynamic data described above demonstrate that the 1.75 mg and 3.5 mg zolpidem lozenges produced rapid sedative-hypnotic effects without the risk of anterograde amnesia or falling in night, which are side-effects typical of higher PO Ambien® doses.
5. The pharmacokinetic and pharmacodynamic response to the low dose zolpidem lozenges was proportional to the dose. Therefore, the pharmacology of zolpidem at a dose range of between about 1 mg to 3.5 mg, unlike that of 5 mg PO Ambien®, is expected to produce a consistent and predictable response.
6. The pharmacodynamic data described above clearly demonstrate the sedative effects of 1.75 mg and 3.5 mg zolpidem lozenge formulations, which included rapid onset of action. In fact, the onset of action and peak effects as defined by both DSST (objective) and VAS (subjective) occurred within 20 minutes. In contrast, 5 mg PO Ambien® produced peak DSST effects in about 60 minutes and the magnitude of the response was only about 50% of that seen with the 3.5 mg zolpidem lozenge. The levels of decline in DSST (surrogate for sedation) scores were comparable to those seen with marketed hypnotics.

7. During the pharmacodynamic portion of the study, low dose zolpidem lozenges containing 1.75 or 3.5 mg zolpidem produced peak sedative effects (as measured by DSST and VAS) within about 20 minutes of dosing.
8. The 3.5 mg zolpidem lozenge also impaired vigilance (as measured by reaction times on PVT). The 1.75 mg zolpidem lozenge had no effect on subjects who were non-elderly adults.
9. None of the doses of zolpidem present in the low dose zolpidem lozenges impaired performance on a memory test (Buschke) or a simple motor task capability test (SCT).

Example 3

Low Dose Zolpidem Tablet Composition

An immediate release peroral (PO) tablet containing a low dose of zolpidem can be prepared according to the formulation set forth in Table 5.

TABLE 5

Low dose zolpidem tablet formulation.

Component	Quantity (mg)
Zolpidem Hemitartrate	3.5
Povidone K29/32	15.0
Sodium Starch Glycolate (SSG)	7.5
Starch 1500	15.0
Lactose Fast Flow	82.0
Prosolv SMCC 90	65.5
Sodium bicarbonate	40
Magnesium Stearate	1.5
Total	230

Manufacturing Process

Dispensing: Screen the zolpidem hemitartrate and excipients through screen #30. Dispense the required quantities of each ingredient.

Blending:

1. Transfer the zolpidem hemitartrate and Povidone K 29/32 to a V-Shell blender and blend for 2 min.
2. Add SSG and Starch 1500 to Step 1 and blend for another 2 min.
3. Add Lactose Fast Flow and Prosolv SMCC 90 to Step 2 and blend for another 10 min.
4. Mix an equal amount of the blend from Step 3 with magnesium stearate or sodium stearyl fumarate and transfer the mixture back to the V-Shell blender via screen #30. Blend for 3 min.

Compression: Compress the final blend from Step 4 on a rotary press to a target tablet weight of 210 mg.

Example 4

Pharmacokinetic and Pharmacodynamic Evaluation of Low Dose Zolpidem Transmucosal Compositions

The purpose of this study was to evaluate, in healthy volunteers after daytime administration, the pharmacodynamic (PD) and pharmacokinetic (PK) profiles and tolerability of sublingual, low-dose, transmucosal zolpidem (ST zolpidem) lozenges compared to placebo.

Methods

Study Design

This study was a single-dose, randomized, double-blind, placebo-controlled, daytime, cross-over study. Three doses of ST zolpidem (1.0, 1.75 and 3.5 mg) were compared with matching placebo in healthy volunteers. The protocol for this study was approved by an institutional review board for the study site and the study itself was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines. Subjects were paid for their participation.

Subject selection included a clinical assessment visit and 7 days of morning sleep diary screening to ensure that all study criteria were met. Subjects were randomized to one of four treatment sequences, which included all 3 doses of active treatment and placebo. Each treatment period consisted of 2 days separated by a washout period of 5 to 12 days.

During each of the 4 treatment periods, subjects were admitted to the site on the evening prior to dosing and had an obligatory 8 hours in bed. The following two mornings, subjects were awakened at a fixed time and, following baseline assessments, received the study drug at 8:00 AM (approximately one hour after awakening). Pharmacodynamic assessments were conducted prior to dosing and over a period of 5 hours after study drug administration on the first morning of treatment. On the second morning, the same treatment was administered and venous blood was drawn prior to dosing and over a period of 12 hours following study treatment administration for pharmacokinetic evaluation.

In each treatment period, subject mobility was limited. Specifically, for the first 5 hours after dose administration participants were required to remain seated unless medically or procedurally necessary. Furthermore, subjects were kept awake until all procedures were completed. Subjects had to pass a heel-to-toe gait test prior to leaving the laboratory.

Subject Recruitment and Selection

Healthy, non-smoking adult men and women, age 21-45 with no current self-reported sleeping problems were eligible for participation in the study. After signing a written informed consent statement and following initial screening, a physical examination, clinical laboratory tests and electrocardiogram, subjects were invited to complete a 7-day sleep diary provided that they did not (1) have any DSM-IV Axis I psychiatric disorders or any circadian rhythm sleep disorder, (2) have a history of substance abuse or substance dependence, (3) have a Epworth Sleepiness Scale score of greater than 12, (4) have had an acute clinically significant illness or surgery, including oral surgery, tooth extraction or piercing of the lip/tongue within 60 days prior to Day 1 of the study, (5) utilize any over-the-counter or prescription medication within two weeks prior to screening, or (6) take any drugs known to induce or inhibit hepatic drug metabolism within 30 days prior to Day 1 of double-blind study medication.

Subjects qualified for randomization if their diaries reported a mean weekly latency to sleep onset of ≦30 minutes, a mean weekly total time in bed of ≧7 hours and a stable bedtime pattern as defined by a usual bedtime between 2200-2400 and a usual rise time between 0500-0800 (neither of which varied by more than 2 hours on 5 of 7 nights).

Study Procedures

Study Drug: The four treatments evaluated were 1.0, 1.75 and 3.5 mg ST zolpidem and placebo lozenges. Subjects were randomized into dosing sequences of four treatment periods (Latin Square) that were separated by 5-12 days. Each subject was randomized into a dosing sequence that included all four treatments. Medication was dispensed by study personnel on each morning in the sleep laboratory at 8 AM.

Subjects were instructed to rinse their mouth with water prior to dosing and then place the lozenge under their tongue until it dissolved. Saliva was swallowed every 2 minutes until the nearest 2 minutes after complete lozenge dissolution. Study personnel performed oral cavity examinations before

and after dosing to ensure consumption of medication and to note any signs of oral irritation.

Pharmacodynamic Assessments: Subjects practiced pharmacodynamic (PD) tests after admission to the laboratory on the night prior to treatment. On the first morning of each treatment period, subjects performed the PD tests immediately before dosing and at 10 minutes (VAS only), 20 minutes, 1, 1.5, 2, 2.5, 3, 4 and 5 hours post-dose. PD tests were always performed in the same order: Digit Symbol Substitution Test (DSST), Choice Reaction Test (CRT), Symbol Copying Test (SCT), subject rating of sedation (VAS) and Word Recall Test.

During the DSST (Kaplan G B, Greenblatt D J, Ehrenberg B L, et al., *J Cli Pharmacol,* 1997; 37:693-703), subjects were given a set of symbols with corresponding single digit numbers and a set of "blank" boxes with corresponding digits. Subjects were asked to make as many symbol-for-digit substitutions as possible working from left to right without skipping any boxes within a 90-second period and the number of correct substitutions was recorded. Throughout the study, subjects completed equivalent DSST variants, with no individual taking the same form more than once.

For the CRT (Roehrs T, Merlotti L, Zorick F, Roth T., *Psychopharmacol* 1994; 116:130-4), subjects were provided with a hand-held device with response buttons for measuring reaction time following the presentation of visual and/or audio stimulus. Response time was defined as the time in milliseconds between the onset of the stimulus and the response button being pressed. The mean response time, the number of errors and the number of lapses (defined as reaction time>500 ms) were evaluated.

During the SCT (Stone B M. *Brit J Clin Pharmacol* 1984; 18 (suppl 1):15S-20S), subjects were given a sheet filled with double rows: the upper row filled with symbols, the lower row empty. Subjects were asked to make as many accurate symbol-copies as possible working from left to right without skipping any boxes within a 90-second period and the number of correct copies was recorded. Throughout the study, subjects completed equivalent SCT variants, with no individual taking the same form more than once.

Finally, acquisition and immediate recall of information was evaluated using a word-list free recall procedure (Shader R I, Dreyfuss D, Gerrein J R et al. *Clin Pharmacol Therap* 1986; 39:526-9). Fifteen words were read in random order at a rate of one word per second, during each test session. Recall was tested immediately after presentation of the list, and subjects were given 1 minute to write down list items recalled in any order. Throughout the study, subjects had to recall equivalent word list variants, with no individual hearing the same list more than once. The number of correct words (ignoring spelling mistakes) was recorded.

Subjective Ratings: Subjects' self-ratings of sedative effects were obtained on a 100 mm visual analog scale (VAS) anchored by '0'="very sleepy" and 100'="wide awake and alert." This type of VAS scale is often used in clinical trials to assay sedative effects (typically as residual effects in the morning).

Pharmacokinetic Sample Collection and Parameters: On the second morning of each treatment period, a total of 18 blood samples were collected. The first sample was collected prior to dosing. Subsequent samples were collected at 5, 10, 20, 30 and 45 minutes and 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10 and 12 hours post-dose. All blood samples were centrifuged within 110 minutes and plasma was separated, divided into 2 duplicate aliquots and frozen until the time of assay. The bioanalytical laboratory analyzed zolpidem in plasma samples using a validated LC/MS/MS method. PK parameters included the area under the plasma concentration curve from time 0 to the last measurable concentration (AUC_{0-1}), the area under the plasma concentration curve from time 0 to infinity (AUC_{0-inf}), the maximum plasma concentration (C_{max}), the time of the maximum plasma concentration (t_{max}), and the apparent terminal elimination half-life ($t_{1/2}$).

Safety Evaluations

Vital signs were recorded at screening, prior to dosing and at scheduled intervals during each treatment period. Subject oral cavities were examined for buccal irritation prior to dosing, at the time of lozenge dissolution, at 15, 30, 60 and 120 minutes post-dissolution and at discharge. A physical examination along with chemistry, hematology and urinalysis were performed at study entry and prior to discharge in the fourth treatment period. All subjects had to pass a heel-to-toe gait test before leaving the clinic.

Statistical Analysis

All analyses performed in this study were defined prior to breaking the study blind. All randomized subjects completed all four treatment periods. Therefore, the intent-to-treat and per-protocol populations were identical. The statistical analyses discussed reflect the full set of 24 randomized patients.

PD values are presented and analyzed as change relative to pre-dose values. Each time point was evaluated separately relative to the baseline value. In addition, area under the time-effect curve for the effect change scores was calculated for defined time intervals.

PK parameters were calculated from the concentration-time data using non-compartmental techniques. Using SAS, ANOVA was performed on untransformed t_{max} and $t_{1/2}$, and on ln-transformed dose normalized values of AUC_{0-t}, AUC_{0-inf} and C_{max} at the alpha level of 0.05. Linearity in PK response of various doses was assessed by applying the power function $P=A*Dose^b$ to non-normalized C_{max} and AUC_{0-t} values of zolpidem.

Safety was assessed by Adverse Events (AEs), vital signs and laboratory parameters. AEs were defined according to the Medical Dictionary for Regulatory Activities (MedDRA®). AEs with onset (or worsening) after the start of study drug were considered treatment-emergent. The frequency of treatment-emergent AEs and the frequency of events by body system were summarized by treatment period according to preferred term and system organ class.

Results

Demographics

A total of 24 subjects were randomized to treatment for this study. All participants completed all four treatment periods; there were no discontinuations. The demographics and sleep histories of the subject population are detailed in Tables 6 and 7. As can be seen, study subjects were healthy and reported no sleep difficulties.

TABLE 6

Subject Demographics

Gender	
Male (%)	13 (54.2)
Female (%)	11 (45.8)
RACE	
Caucasian (%)	15 (62.5)
African-American (%)	9 (32.5)
Age	
Mean (SD)	34.7 (7.1)
Range	21-44

TABLE 6-continued

Subject Demographics	
Weight (kg)	
Mean (SD)	74.4 (10.8)
Range	51.7-100.2
BMI	
Mean (SD)	24.9 (2.8)
Range	19-30

TABLE 7

Subject Sleep History	
Usual Time in Bed (hr)	
Mean (SD)	8.2 (0.4)
Range	8.0-9.0
Usual Time to Fall Asleep (min)	
Mean (SD)	13.0 (5.4)
Range	3.0-25.0
Usual Sleep Time During Night (hr)	
Mean (SD)	8.1 (0.4)
Range	7.5-9.0
Usual Time Awake During Night (min)	
Mean (SD)	2.3 (2.8)
Range	0.0-10.0
Usual Number of Nocturnal Awakenings	
0	13
1	10
2	1
Epworth Sleepiness Scale	
Mean (SD)	3.5 (2.6)
Range	0.0-11.0

Psychomotor Performance

The sedative effects of ST zolpidem lozenges were assessed by multiple PD evaluations, including DSST, CRT, SCT, and Word Recall as well as by subjective self-rating of sedation by VAS. On the pre-drug performance sessions, no significant treatment differences were observed on any of these endpoints. During post-drug performance, in comparison to placebo, all measures were significantly affected by at least one dose of ST zolpidem.

DSST scores at individual time points indicated significant psychomotor impairment by ST zolpidem 3.5 and 1.75 mg as early as 20 minutes post-intake (FIG. **8**). Significant reduction in DSST scores lasted up to 90 minutes post-dose (3.5 mg), and performance after ST zolpidem was no longer distinguishable from placebo on any endpoint as early as at the 3-hour time point. These observations were confirmed by partial I-hour effect-area measures (FIG. **9**). There was significant impairment compared to placebo for ST zolpidem 1.75 mg and 3.5 mg during the (0-1)-hour time period, while there was no longer any difference during the (4-5)-hour time period. ST zolpidem 1-mg had no measurable effect by either analysis, in this patient population.

Relevant characteristics of the other PD evaluations are summarized in Table 8. Overall, it is readily apparent that ST zolpidem at the 1 mg dose has no measurable effect on any parameter (except at one time point measuring the number of errors in CRT), whereas ST zolpidem 3.5 mg impacts all outcome measures, albeit for different time periods. Based on these tests, the time of maximum impairment by ST zolpidem 1.75 and 3.5 mg ranges from 20 minutes to 3 hours post-dose, and time post-drug where the measured parameters no longer differed from placebo ranged from 1 hour to 4 hours.

Specifically, onset of impairment of CRT was found to be as early as the other PD outcomes, but duration was differentially affected depending on the specific parameter. Actual reaction time was significantly prolonged by zolpidem 3.5 mg at the early time points only and was no longer different from placebo at 2 hours post-drug administration. The number of lapses was affected by both 3.5 and 1.75 mg ST zolpidem, with peak effect for both at 20 minutes, but duration of impairment was longer for the 3.5 mg than the 1.75 mg dose, 2.5 hr and 1.0 hr, respectively. The number of errors committed during CRT measures was found to be somewhat variable. The 3.5 mg dose was associated with the longest duration of impairment with a peak effect at 3 hours and subsequently, no statistical difference from placebo at 4 hours. Although the 1.75 mg dose did not differ at any time point from placebo, there was one statistically significant increase in the number of errors after the 1 mg dose, occurring at the 1-hour time point (Table 8).

The two higher doses of ST zolpidem, i.e., 3.5 mg and 1.75 mg, significantly impaired fine motor activity as measured by SCT, with impairment due to the higher dose lasting 30 minutes longer than the lower, 1.5 hrs versus 1 hr, respectively (Table 8).

Lastly, in terms of memory, compared to placebo, immediate free recall was significantly impaired by ST zolpidem 3.5 mg at 20 minutes post-ingestion and this effect was no longer detectable one hour later. No measurable effect was observed with the two lower doses of ST zolpidem (Table 8).

TABLE 8

Effect of ST zolpidem on Daytime Pharmacodynamic Assessments

Parameter	ST zolpidem Dosage (mg)	Maximum change relative to placebo	p-value	Time of maximum change	Time no longer different from placebo
Word Recall	3.5	1.2	0.0387	20 min	1 hr
(# words)	1.75	1.0	N.S.	1 hr, 2 hr	N.A.
	1.0	0.6	N.S.	1 hr	N.A.
CRT	3.5	234.7	<0.0001	20 min	2 hr
(reaction	1.75	103.3	N.S.	1 hr	N.A.
time, ms)	1.0	85.7	N.S.	1 hr	N.A.
CRT	3.5	13.6	<0.0001	20 min	2.5 hr
(# lapses)	1.75	5.6	0.0199	20 min	1 hr
	1.0	4.3	N.S.	1 hr	N.A.
CRT	3.5	5.1	0.0225	3 hr	4 hr
(# errors)	1.75	3.1	N.S.	2.5 hr	N.A.
	1.0	6.8	0.0419	1 hr	1.5 hr
SCT	3.5	14.8	<0.0001	20 min	2.0 hr
	1.75	7.6	0.0011	1 hr	1.5 hr
	1.0	3.0	N.S.	1 hr	N.A.

Subjective Ratings

Self-ratings of sedation by the VAS exhibited a pattern similar to that observed for DSST (FIG. **10**). Subjects did not feel sedated at 10 minutes post-drug intake, but rated themselves significantly sedated compared to placebo from 20 minutes through 2 hours post-drug at the 1.75 and 3.5 mg dose levels. The ratings remained different from placebo for up to 3 hours, but were no longer statistically significantly different, primarily due to progressively increased sedation rating in the placebo condition.

Pharmacokinetics

Descriptive statistics for the PK parameters are presented by dose in Table 9. Over the dose range and time periods

studied, mean C_{max} and mean AUC values were proportional to dose. Mean t_{max} and mean elimination half-life were equivalent across treatment, conditions. Plasma concentration-time profiles following ST zolpidem administration are presented in FIG. **11**. Zolpidem plasma levels of >20-25 ng/ml were reached within 20 minutes after both 1.75 and 3.5 mg ST zolpidem administration and were maintained for up to 4 hours. Zolpidem was no longer detectable 12 hours after administration.

TABLE 9

Mean pharmacokinetic parameters (SD) of ST zolpidem

	1.0 mg	1.75 mg	3.5 mg
C_{max} (ng/ml)	17.03 (6.84)	32.17 (10.38)	64.14 (22.36)
Range C_{max}	0-35.51	9.33-60.33	19.85-125.96
$t_{1/2}$ (hr)	2.33 (0.79)	2.43 (0.60)	2.45 (0.58)
$AUC_{0\text{-}inf}$ (ng * hr/ml)	66.16 (31.49)	126.10 (53.39)	242.57 (100.37)
t_{max} (min)	35.7 (12.7)	37.9 (16.1)	37.9 (12.3)

Safety

The ST zolpidem lozenges were generally safe and well tolerated. Subjects experienced a total of 48 adverse events, most of which were related to the clinical effect of the drug-sedation and were mild to moderate in severity (Table 10). Side effect appeared only at the high dose, with 10 Subjects reporting sedation at 3.5 mg compared to 3 for placebo. Dizziness, nausea and headache peaked at the 3.5 mg dose level (3, 3 and 2 subjects, respectively), with fewer instances seen with the 1.75 mg dose (1, 0, and 2 subjects) and no reports of these conditions at either the 1.0 mg level or placebo. Only one event (epigastric pain) was severe and was judged unrelated to treatment (1.75 mg lozenge) by the investigator. Two adverse events not related to treatment (headache: 1.75 mg lozenge, dysmenorrhoea: placebo) were treated with Tylenol or ibuprofen. All other events resolved without treatment.

TABLE 10

Adverse Events Occurring in ≧5% of Subjects

Variable	Placebo	1.0 mg	1.75 mg	3.5 mg
Somnolence	3 (12.5%)	5 (20.8%)	3 (12.5%)	10 (41.7%)
Fatigue	6 (25.0)	2 (8.3)	8 (33.3)	4 (16.7)
Dizziness	—	—	1 (4.2)	3 (12.5)
Nausea	—	—	—	3 (12.5)
Headache	—	—	1 (4.2)	2 (8.3)

Conclusions

It is noteworthy that this study was conducted in normal sleepers with zolpidem intake early in the morning subsequent to a full night's sleep. Although in this study, no direct comparison was included with zolpidem 5, or 10 mg in standard oral formulations, published observations of very similar study design indicate that following the 10 mg zolpidem dose, measurable performance deficit occurs at 1 hour post-intake and is of similar magnitude as measured here for the 3.5 mg dose (Greenblatt D J, Harmatz J S, von Moltke L L, et al. *Clin Pharmacol Ther* 1998; 64:553-61). Thus, it appears that sedative effects of sublingual zolpidem occurred at a dose and an earlier time of less than half of those reported for oral zolpidem 10 mg (Ambien® 10 mg). Within the ST zolpidem dose range investigated in this study (1 mg to 3.5 mg), there was a reasonable dose-effect relationship with 3.5 mg showing the greatest sedative potential and 1.75 mg as the lowest active dose. The sublingual dose of 1 mg can be considered a no-effect ST zolpidem dose, in this non-elderly patient population.

The PK profile of ST zolpidem lozenges is characterized by very rapid absorption with mean peak concentrations of 17.8 (range 0-35.5), 32.2 (range 9.3-60.3), and 64.1 (range 19.9-125.9) ng/ml for 1.0, 1.75, and 3.5 mg of ST zolpidem, respectively, occurring at approximately 37 (range 36 to 37.9) minutes post-administration. In comparison, currently available oral zolpidem tablets (Ambien®) are reported to attain peak concentrations (C_{max}) of 59 (range 29 to 113) and 121 (range 58 to 272) ng/ml for 5 and 10 mg respectively, at a mean time (t_{max}) of 1.6 hours for both (Med Lett Drugs Ther 2005; 47 (1223-4):97-9; Roehrs T, Merlotti L, Zorick F, Roth T. *Psychopharmacol* 1994; 116:130-4; Stone B M. *Brit J Clin Pharmacol* 1984; 18 (suppl 1):15S-20S; Shader R I, Dreyfuss D, Gerrein J R et al. *Clin Pharmacol Therap* 1986; 39:526-9). Thus, t_{max} for ST zolpidem occurs at a time less than half of that reported of the oral zolpidem tablets.

In addition, within 20 minutes post-dose, ST zolpidem 1.75 and 3.5 mg achieved plasma zolpidem levels greater than 20 to 25 ng/ml, the estimated levels for onset and offset of sedation (Patat A, Trocheries S, Thebault J J et al. *Psychopharmacol* (Berlin) 1994; 114: 138-46). These reportedly clinically relevant zolpidem blood levels are paralleled by the PD observations of sedative activity, specifically the effects on DSST scores and subjective ratings of sedation. ST zolpidem did not alter the elimination half-life of zolpidem: $t_{1/2}$ of ST zolpidem (2.3, 2.4, and 2.5 hours for 1, 1.75, and 3.5 mg, respectively) is very much in agreement with that reported for oral zolpidem tablets (2.5 and 2.6 hours for 5 and 10 mg, respectively).

ST zolpidem lozenges were found to be generally safe and well tolerated. The side effect profile was consistent with the low-dose sedative-hypnotic effects of zolpidem.

Taken together, these results show that ST zolpidem 3.5 mg produced sedative activity similar to the sedative effects reported for 10 mg oral zolpidem. Furthermore, the maximal sedative effect as measured by DSST produced by ST zolpidem was observed as early as twenty minutes post-dose as compared to sixty minutes post-dose reported for 10 mg oral zolpidem. These pharmacodynamic effects of ST zolpidem may be related to its pharmacokinetics as suggested by a shorter t_{max} for ST zolpidem than that reported for 10 mg oral zolpidem. Lastly, ST zolpidem produced rapid clinically relevant blood levels which persisted for 2 to 4 hours which were paralleled with PD assays sedative activity. It may be concluded that these characteristics make ST zolpidem an ideal candidate for the pro re nata ("as needed") treatment of sleep maintenance insomnia characterized by prolonged wakefulness after middle of the night awakenings.

All publications and patent applications cited in this specification are herein incorporated by reference as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference. Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

What is claimed is:

1. A solid unit dosage composition for the treatment of MOTN insomnia, said composition comprising an effective amount of zolpidem or a salt thereof, formulated for delivery of zolpidem across a subject's oral mucosa, wherein said effective amount is an amount of less than 1.30×10^{-5} moles of zolpidem, and is an amount sufficient to produce a plasma concentration between about 25 ng/ml and about 50 ng/ml within 20 minutes of administration, when evaluated in an appropriate patient population.

2. The solid unit dosage composition of claim **1**, which further provides 50% of the maximum plasma concentration (Cmax) of zolpidem in 10 minutes or less.

3. The solid unit dosage composition of claim **2**, which further provides blood levels of zolpidem that are less than 20 ng/ml at a time 4 hours after dosing.

4. The solid unit dosage composition of claim **1**, further comprising at least one pH-adjusting agent selected from the group consisting of a carbonate salt and a bicarbonate salt.

5. The solid unit dosage composition of claim **1**, further comprising a binary buffer system that raises the pH of said subject's saliva to a pH greater than about 8.5, irrespective of the starting pH of saliva.

6. The solid unit dosage composition of claim **5**, wherein the binary buffer system consists of sodium carbonate and sodium bicarbonate.

7. The solid unit dosage composition of claim **6**, in the form of a quick-dissolving tablet or lozenge.

8. The solid unit dosage composition of claim **5**, containing from 0.5 to 4.75 mg of zolpidem hemitartrate.

9. The solid unit dosage composition of claim **5**, containing from 1.5 to 2.5 mg of zolpidem hemitartrate.

10. The solid unit dosage composition of claim **5**, containing from 3.0 to 3.75 mg of zolpidem hemitartrate.

11. The solid unit dosage composition of claim **1**, wherein the zolpidem is delivered across at least one of the sublingual or buccal mucosa.

12. A solid unit dosage composition for the treatment of MOTN insomnia, said composition comprising an effective amount of zolpidem or a salt thereof and at least one buffering agent, formulated for delivery of zolpidem across a subject's oral mucosa, wherein said effective amount is 0.5 to 4.75 mg of zolpidem hemitartrate, and is an amount sufficient to produce a plasma concentration between about 25 ng/ml and about 50 ng/ml within 20 minutes of administration, when evaluated in an appropriate patient population.

13. The solid unit dosage composition of claim **12**, wherein the solid unit dosage form dissolves in about 2 minutes or less in the subject's mouth.

14. The solid unit dosage composition of claim **12**, wherein at least about 25% by weight of the solid unit dosage form dissolves within about 5 minutes.

15. The solid unit dosage composition of claim **1**, wherein the solid unit dosage form dissolves in about 2 minutes or less in the subject's mouth.

16. The solid unit dosage composition of claim **1**, wherein at least about 25% by weight of the solid nit dosage form dissolves within about 5 minutes.

17. The solid unit dosage composition as in any of claims **1-6**, **15**, or **16**, containing about 1.75 mg of zolpidem hemitartrate.

18. The solid unit dosage composition as in any of claims **1-6**, **15**, or **16**, containing about 3.5 mg of zolpidem hemitartrate.

19. The solid unit dosage composition of claim **12**, which thither provides 50% of the maximum plasma concentration (Cmax) of zolpidem in 10 minutes or less.

20. The solid unit dosage composition of claim **19**, which further provides blood levels of zolpidem that are less than 20 ng/ml at a time 4 hours after dosing.

21. The solid unit dosage composition of claim **12**, further comprising at least one pH-adjusting agent selected from the group consisting of a carbonate salt and a bicarbonate salt.

22. The solid unit dosage composition of claim **12**, further comprising a binary buffer system that raises the pH of said subject's saliva to a pH greater than about 8.5, irrespective of the starting pH of saliva.

23. The solid unit dosage composition of claim **22**, wherein the binary buffer system consists of sodium carbonate and sodium bicarbonate.

24. The solid unit dosage composition of claim **23** in the form of a quick-dissolving tablet or lozenge.

25. The solid unit dosage composition as in any of claims **12**, **13**, **14**, **19**, **20**, **21**, **22**, **23**, or **24**, containing about 1.75 mg of zolpidem hemitartrate.

26. The solid unit dosage composition as in any of claim **12**, **13**, **14**, **19**, **20**, **21**, **22**, **23**, or **24**, containing about 3.5 mg of zolpidem hemitartrate.

* * * * *