Michael Dore
Stephen R. Buckingham
LOWENSTEIN SANDLER, PC
65 Livingston Avenue
Roseland, New Jersey 07068
Tel: (973) 597-2500

Attorneys for Plaintiffs Purdue Pharmaceutical Products L.P., Purdue Pharma L.P., and Transcept Pharmaceuticals, Inc.

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. NOVEL LABORATORIES, 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 Novel Laboratories, Inc. ("Novel") 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 Novel Laboratories, Inc. is a Delaware corporation with its principal place of business at 400 Campus Drive, Somerset, NJ 08873.

5. Upon information and belief, Novel is in the business of developing, manufacturing, marketing, distributing, and directly and/or indirectly selling generic pharmaceutical products throughout the United States, including in this judicial district.

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. 7,682,628 (the "'628 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 Defendant by virtue of its widespread and continuous contacts with the state of New Jersey. Among other things, Novel's principal

place of business is in New Jersey. Upon information and belief, Novel's Somerset, New Jersey facility consists of a cGMP manufacturing plant, packaging area, laboratories, warehousing areas, and corporate offices. Novel is registered to do business in New Jersey under Business I.D. No. 0100971912, and is registered as a manufacturer and wholesaler of drugs under Registration No. 5003657.

9. Novel 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.*, *Salix Pharms., Inc. et al. v. Novel Labs., Inc.*, Civ. A. No. 3:08-cv-02311-FLW-TJB (D.N.J.) (Dkt. No. 9) (counterclaim filed by Novel); *Salix Pharms., Inc. v. Novel Labs., Inc. et al.*, Civ. A. No. 3:08-cv-4638-FLW-JJH (D.N.J.) (Dkt. No. 21) (same); *Braintree Labs., Inc. v. Novel Labs., Inc.*, Civ. A. No. 3:11-cv-01341-GEB-TJB (D.N.J.) (Dkt. No. 11) (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 No. 7,682,628 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 '628 Patent. Purdue Pharma L.P. and Purdue Pharmaceutical Products L.P. are exclusive licensees under the '628 Patent, the former to sell or offer to sell, and the latter to manufacture, zolpidem tartrate sublingual tablets.

ANDA No. 204299

18. Upon information and belief, on or before July 30, 2012, Novel submitted to FDA an ANDA (ANDA No. 204299) 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. 204299 for the 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, Novel sent Plaintiffs Purdue Pharma L.P. and Transcept Pharmaceuticals, Inc. a letter with a U.S. Postal Service envelope dated July 26, 2012 (the "Notice Letter"). The Notice Letter represented that Novel had submitted to FDA ANDA No. 204299 with a paragraph IV certification for the '628 Patent.

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, Novel's purpose in

submitting ANDA No. 204299 is to market products described therein before expiration of the '628 Patent.

Count 1: Patent Infringement of the '628 Patent

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

23. United States Patent No. 7,682,628, entitled "COMPOSITIONS FOR DELIVERING HYPNOTIC AGENTS ACROSS THE ORAL MUCOSA AND METHODS OF USE THEREOF," was duly and legally issued by the United States Patent and Trademark Office on March 23, 2010. Plaintiff Transcept Pharmaceuticals, Inc. is the owner of the '628 Patent. Plaintiffs Purdue Pharmaceutical Products L.P. and Purdue Pharma L.P. are exclusive licensees of the '628 Patent. A true and complete copy of the '628 Patent is attached hereto as Exhibit B.

24. Upon information and belief, Novel submitted ANDA No. 204299 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 '628 Patent.

25. Novel's manufacture, use, offer for sale, or sale of such product would infringe the claims of the '628 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 Novel's ANDA No. 204299 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 '628 Patent. Upon information and belief, this infringement will occur at Novel's behest, with its intent, knowledge,

and encouragement, and Novel will actively induce, encourage, aid, and abet this administration with knowledge that it is in contravention of Plaintiffs' rights under the '628 Patent.

27. Novel'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. 204299 would actively induce and contribute to infringement of the '628 Patent, and Novel 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, Novel purportedly provided written certification to FDA that the claims of the '628 Patent are invalid and/or will not be infringed by the manufacture, use, or sale of Novel's generic version of INTERMEZZO®.

29. Upon information and belief, Novel gave written notice of its certification of invalidity and/or non-infringement of the '628 Patent, alleging that claims of the '628 Patent are invalid and that claims 10, 11, and 13 would not be infringed by Novel's generic version of INTERMEZZO®, and informing Plaintiffs that Novel seeks approval to engage in the commercial manufacture, use, and sale of a product bioequivalent to INTERMEZZO® prior to the expiration of the '628 Patent.

30. Novel has infringed the '628 Patent under 35 U.S.C. § 271(e)(2)(A) by virtue of submitting ANDA No. 204299 with a paragraph IV certification and seeking FDA approval of ANDA No. 204299 to market a generic version of INTERMEZZO® prior to the expiration of the '628 Patent. Moreover, if Novel commercially uses, offers for sale, or sells its generic version of INTERMEZZO®, or induces or contributes to such conduct, it would further infringe the '628 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 Novel is not enjoined from infringing or actively inducing or contributing to infringement of the '628 Patent. Plaintiffs do not have an adequate remedy at law.

Prayer for Relief

WHEREFORE, Plaintiffs seek the following relief:

A. A judgment that Defendant has infringed the '628 Patent 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 FDA approval of ANDA No. 204299 is not earlier than the expiration date of the '628 Patent, or any later expiration of exclusivity for the '628 Patent to which Plaintiffs are or become entitled;

C. A permanent injunction restraining and enjoining Defendant 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 '628 Patent, including the product described in ANDA No. 204299;

D. A judgment declaring that making, using, selling, offering to sell, or importing the product described in ANDA No. 204299, or inducing or contributing to such conduct, would constitute infringement of the '628 Patent by Defendant 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: September 10, 2012

Respectfully submitted,

/s/ Michael Dore
Michael Dore
Stephen R. Buckingham
LOWENSTEIN SANDLER, PC
65 Livingston Avenue
Roseland, N.J. 07068
Tel: (973) 597-2500

Attorneys for Plaintiffs Purdue Pharmaceutical Products L.P., Purdue Pharma L.P., and Transcept Pharmaceuticals, Inc.

Of Counsel:
Christopher N. Sipes
Michael N. Kennedy
Erica N. Andersen
COVINGTON & BURLING LLP
1201 Pennsylvania Avenue, N.W.
Washington, D.C. 20004
Tel: (202) 662-6000

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 United States Patent on which this Complaint is based is the subject of two patent infringement actions recently filed in this District, *Purdue Pharmaceutical Products, Inc. et al. v. Actavis Elizabeth LLC*, 12-CV-5311-JLL-MAH, and *Purdue Pharmaceutical Products, Inc. et al. v. Watson Pharmaceuticals, Inc. et al.*, 12-CV-5390-JLL-MAH, both of which have been assigned to the Honorable Jose L. Linares.

/s/ Michael Dore
Michael Dore
Stephen R. Buckingham
LOWENSTEIN SANDLER, PC
65 Livingston Avenue
Roseland, N.J. 07068
Tel: (973) 597-2500

Attorneys for Plaintiffs Purdue Pharmaceutical Products L.P., Purdue Pharma L.P., and Transcept Pharmaceuticals, Inc.

Dated: September 10, 2012

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

---

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.

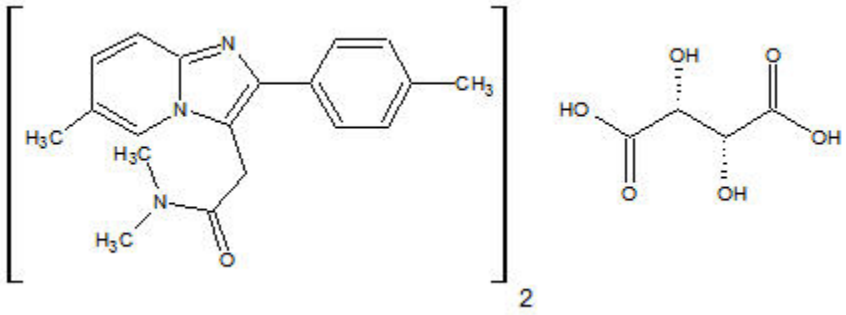
As with management of all overdosage, the possibility of multiple drug ingestion should be considered. The healthcare provider may wish to consider contacting a poison control center for up-to-date information on the management of hypnotic drug overdosage.

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).

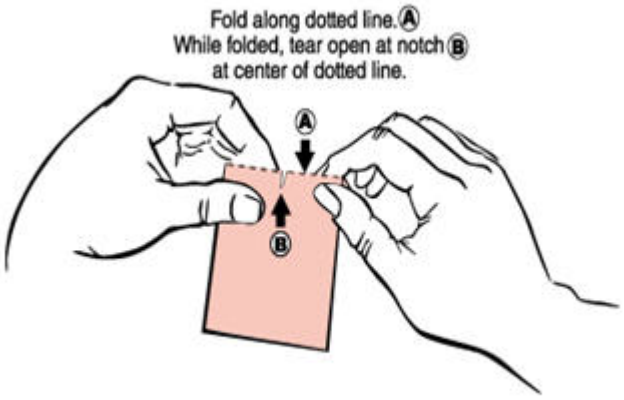


Figure D

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).

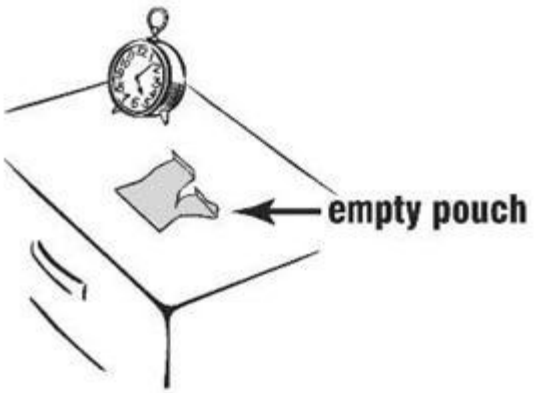


Figure F

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.

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

Issued: July 2012

Revised: 07/2012 Purdue Pharma LP

EXHIBIT B

US007682628B2

(12) **United States Patent**
Singh

(10) **Patent No.: US 7,682,628 B2**
(45) **Date of Patent: *Mar. 23, 2010**

(54) **COMPOSITIONS FOR DELIVERING HYPNOTIC AGENTS ACROSS THE ORAL MUCOSA AND METHODS OF USE THEREOF**

(75) Inventor: **Nikhilesh N. Singh**, Mill Valley, 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 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **11/833,323**

(22) Filed: **Aug. 3, 2007**

(65) **Prior Publication Data**

US 2008/0008753 A1 Jan. 10, 2008

Related U.S. Application Data

(63) Continuation of application No. 11/060,641, filed on Feb. 16, 2005.

(60) Provisional application No. 60/598,629, filed on Aug. 3, 2004, provisional application No. 60/608,957, filed on Feb. 17, 2004.

(51) **Int. Cl.**
A61K 9/20 (2006.01)
A61F 13/00 (2006.01)

(52) **U.S. Cl.** **424/464**; 424/434; 424/435

(58) **Field of Classification Search** ..... None
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,382,938 A 5/1983 Kaplan et al.
4,405,647 A 9/1983 Fisher et al.
4,460,592 A 7/1984 Kaplan et al.

(Continued)

FOREIGN PATENT DOCUMENTS

WO WO 99/16417 4/1999

(Continued)

OTHER PUBLICATIONS

Danjou et al., "A comparison of the residual effects of zaleplon and zolpidem following administration 5 to 2 hours before awakening." Br. J. Clin. Pharmacology 48:367-374 (Jun. 1999).

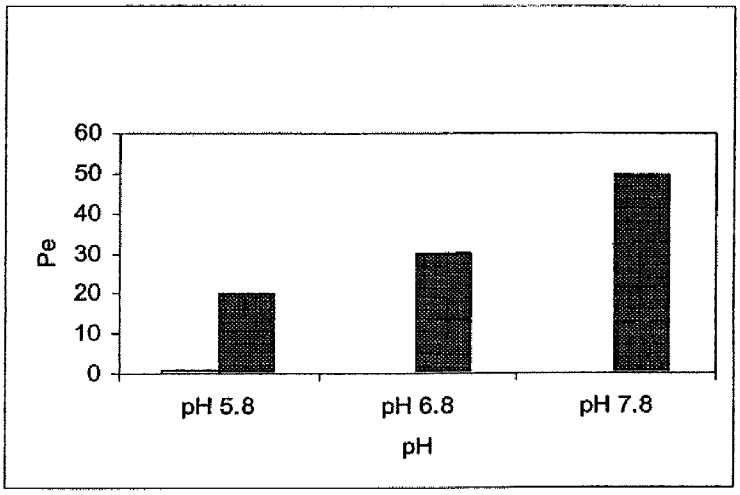
(Continued)

Primary Examiner—Humera N Sheikh
(74) *Attorney, Agent, or Firm*—O'Melveny & Myers LLP

(57) **ABSTRACT**

The present invention provides novel compositions for the delivery of a hypnotic agent across the oral mucosa. In particular, the buffer system in the compositions of the present invention raises the pH of saliva to a pH greater than about 7.8, thereby facilitating the substantially complete conversion of the hypnotic agent from its ionized to its un-ionized form. As a result, the dose of hypnotic agent is rapidly and efficiently absorbed by the oral mucosa with surprisingly low inter-subject variability. Furthermore, delivery of the hypnotic agent across the oral mucosa advantageously bypasses hepatic first pass metabolism of the drug and avoids enzymatic degradation of the drug within the gastrointestinal tract. Methods for using the compositions of the present invention for treating sleep disorders such as insomnia are also provided.

17 Claims, 10 Drawing Sheets



U.S. PATENT DOCUMENTS

4,808,594	A	2/1989	George et al.	
4,863,737	A	9/1989	Stanley et al.	
5,132,114	A	7/1992	Stanley et al.	
5,178,878	A	1/1993	Wehling et al.	
5,223,264	A	6/1993	Wehling et al.	
5,284,659	A	2/1994	Cherukuri et al.	
5,288,497	A	2/1994	Stanley et al.	
5,288,498	A	2/1994	Stanley et al.	
5,503,846	A	4/1996	Wehling et al.	
5,576,014	A	11/1996	Mizumoto	
5,686,094	A	11/1997	Acharya	
5,719,197	A	2/1998	Kanios et al.	
5,785,989	A	7/1998	Stanley et al.	
5,855,908	A	1/1999	Stanley et al.	
5,869,082	A	2/1999	Dugger, III	
5,895,664	A	4/1999	Cherukuri et al.	
5,955,098	A	9/1999	Dugger, III	
5,965,162	A	10/1999	Fuisz et al.	
6,024,981	A	2/2000	Khankari et al.	
6,110,486	A	8/2000	Dugger, III	
6,197,334	B1	3/2001	Renda	
6,200,604	B1	3/2001	Pather et al.	
6,210,699	B1	4/2001	Acharya et al.	
6,211,392	B1	4/2001	Fang et al.	
6,218,397	B1	4/2001	Chen	
6,242,460	B1	6/2001	Ettema et al.	
6,264,981	B1	7/2001	Zhang et al.	
6,264,987	B1	7/2001	Wright et al.	
6,280,770	B1	8/2001	Pather et al.	
6,344,222	B1	2/2002	Cherukuri et al.	
6,348,485	B1	2/2002	Ohkawa et al.	
6,350,470	B1	2/2002	Pather et al.	
6,358,060	B2	3/2002	Pinney et al.	
6,368,625	B1	4/2002	Siebert et al.	
6,383,471	B1	5/2002	Chen et al.	
6,391,335	B1	5/2002	Pather et al.	
6,441,018	B2	8/2002	Faraci et al.	
6,509,036	B2	1/2003	Pather et al.	
6,514,531	B1 *	2/2003	Alaux et al.	424/468
6,569,463	B2	5/2003	Patel et al.	
6,576,250	B1	6/2003	Pather et al.	
6,586,478	B2 *	7/2003	Ackman et al.	514/738
6,589,556	B2	7/2003	Cherukuri	
6,624,162	B2	9/2003	Gymer et al.	
6,638,535	B2	10/2003	Lemmens et al.	
6,641,838	B2	11/2003	Pather	
6,645,528	B1	11/2003	Straub	
6,656,492	B2	12/2003	Kajiyama	
6,676,931	B2	1/2004	Dugger, III	
6,692,771	B2	2/2004	Pather et al.	
6,720,001	B2	4/2004	Chen et al.	
6,733,781	B2	5/2004	Abu-Izza	
6,753,011	B2 *	6/2004	Faour	424/473
6,759,059	B1	7/2004	Pettersson et al.	
6,761,910	B1	7/2004	Pettersson et al.	
6,764,696	B2	7/2004	Pather et al.	
6,893,654	B2	5/2005	Pinney et al.	
6,923,988	B2	8/2005	Patel et al.	
6,969,508	B2	11/2005	Dugger, III	
6,977,070	B2	12/2005	Dugger, III	
6,998,110	B2	2/2006	Dugger, III	
7,118,765	B2	10/2006	Norman	
7,163,705	B2	1/2007	Johnson et al.	
2001/0051186	A1	12/2001	Acharya et al.	
2002/0077332	A1	6/2002	Aronhime	
2002/0098264	A1	7/2002	Cherukuri et al.	
2003/0077227	A1	4/2003	Dugger, III	
2003/0077228	A1	4/2003	Dugger, III	
2003/0077229	A1	4/2003	Dugger, III	
2003/0082107	A1	5/2003	Dugger, III	
2003/0091629	A1	5/2003	Pather et al.	
2003/0095925	A1	5/2003	Dugger, III	
2003/0095926	A1	5/2003	Dugger, III	
2003/0095927	A1	5/2003	Dugger, III	
2003/0124184	A1	7/2003	Mezaache et al.	
2003/0185761	A1	10/2003	Dugger, III	
2003/0185884	A1	10/2003	Singh et al.	
2003/0190286	A1	10/2003	Dugger, III	
2003/0211047	A1	11/2003	Dugger, III	
2003/0232080	A1	12/2003	Pather et al.	
2004/0062716	A1	4/2004	Dugger, III	
2004/0109890	A1	6/2004	Sugimoto	
2004/0120895	A1	6/2004	Dugger, III	
2004/0120896	A1	6/2004	Dugger, III	
2004/0136913	A1	7/2004	Dugger, III	
2004/0136914	A1	7/2004	Dugger, III	
2004/0136915	A1	7/2004	Dugger, III	
2004/0141923	A1	7/2004	Dugger, III et al.	
2004/0185097	A1	9/2004	Kanman et al.	
2004/0213855	A1	10/2004	Pettersson	
2004/0258750	A1	12/2004	Alaux et al.	
2004/0265239	A1	12/2004	Dugger, III et al.	
2004/0265375	A1	12/2004	Platteeuw et al.	
2005/0002867	A1	1/2005	Dugger, III	
2005/0025712	A1	2/2005	Dugger, III	
2005/0025713	A1	2/2005	Dugger, III	
2005/0025714	A1	2/2005	Dugger, III	
2005/0025715	A1	2/2005	Dugger, III	
2005/0025716	A1	2/2005	Dugger, III	
2005/0025717	A1	2/2005	Dugger, III	
2005/0031677	A1	2/2005	Pather et al.	
2005/0037072	A1	2/2005	Pather et al.	
2005/0038042	A1	2/2005	Codd et al.	
2005/0042281	A1	2/2005	Singh et al.	
2005/0142197	A1	6/2005	Moe	
2005/0142198	A1	6/2005	Moe	
2005/0147666	A1	7/2005	Ohta	
2005/0164987	A1	7/2005	Barberich	
2005/0226925	A1	10/2005	Singh	
2005/0281752	A1	12/2005	Dugger	
2006/0216352	A1	9/2006	Nystrom et al.	
2007/0037843	A1	2/2007	Aronhime	
2008/0132517	A1	6/2008	Chow	
2008/0145425	A1	6/2008	Marija	
2008/0262025	A1	10/2008	Kumar	
2008/0287456	A1	11/2008	Roberts	
2008/0311208	A1	12/2008	Pettersson	

FOREIGN PATENT DOCUMENTS

WO	WO 99/63977	12/1999
WO	WO 00/16750	3/2000
WO	WO 00/33835	6/2000
WO	WO 00/38649	7/2000
WO	WO 01/89476	11/2001
WO	WO 2005/032519	4/2005
WO	WO 2006/046041	5/2006

OTHER PUBLICATIONS

Hindmarch et al., "Residual effects of zaleplon and zolpidem following middle of the night administration five hours to one hour before awakening." Human Psychopharmacology 16: pp. 159-167 (2001).

Werth et al., "Dynamics of the sleep EEG after an early evening nap: experimental data and simulations." American Physiological Society pp. R501-R510 (1996).

Hindmarch et al., "Comparison of the residual effects of zaleplon and zolpidem after administration during the night." European Neuropsychopharmacology 10(suppl. 3): s394 Abstract No. P.6.026 (Sep. 2000).

Hoehns and Perry. "Zolpidem: A nonbenzodiazepine hypnotic for treatment of insomnia." Clin. Pharmacy 12: 814-28 (Nov. 1993).

Zhang et al. "Oral Mucosal Drug Delivery—Clinical Pharmacokinetics and Therapeutic Applications." Drug Delivery Systems 41(9): 661-80 (2002).

Patat et al., "EEG profile of intravenous zolpidem in healthy volunteers." Psychopharmacology 114:138-146 (1994).

Roth et al., "Daytime pharmacodynamic and pharmacokinetic evaluation of low-dose sublingual transmucosal zolpidem hemitartrate." Hum. Psychopharmacol. Clin. Exp. 23: 13-20 (2008).

Roth et al., "Low-Dose Sublingual Zolpidem Tartrate is Associated with Dose-Related Improvement in Sleep Onset and Duration in Insomnia Characterized by Middle-of-the-Night (MOTN) Awakenings," *Sleep*, 31(9)1277-1284(2008).

"Ambien® (zolpidem tartrate)" Sanofi-Synthelabo, Inc. ZPSS-5A (Jun. 2002).

Avdeef, A. "Physiochemical Profiling (Solubility, Permeability and Charge State)" Current Topics in Medicinal Chemistry vol. 1 No. 4: 277-351 (2001).

Doghramji, K. "The Need for Flexibility in Dosing of Hypnotic Agents" Sleep 23 (Supplement 1): S16-S22 (2000).

Fry, J. "Zaleplon improves sleep without producing rebound effects in outpatients with insomnia" International Clinical Pharmacology 15(3): 141-152 (2000).

Galey, W. "The InVitro Permeability of Skin and Buccal Mucosa to Selected Drugs and Tritiated Water." The Journal of Investigative Dermatology vol. 67, No. 6: 713-717 (1976).

Gandhi, R. "Bioadhesion in Drug Delivery." Indian Journal of Pharmaceutical Sciences 50(3): 145-152 (1988).

Greenblatt, D. "Comparative kinetics and dynamics of zalepon, zolpidem, and placebo" Clinical Pharmacolology & Therapeutics vol. 64, No. 5: 553-561 (Nov. 1998).

Greenblatt, D. "Kinetic and dynamic interaction study of zolpidem with ketoconazole, itraconazole, and fluconazole" Clinical Pharmacology & Therapeutics vol. 64, No. 6661-671 (Dec. 1998).

Harris, D. "Drug Delivery via the Mucous Membranes of the Oral Cavity" Journal of Pharmaceutical Sciences vol. 81, No. 1: 1-10 (Jan. 1992).

Holm, K. "Zolpidem: An update of its Pharmacology, Therapeutic Efficacy and Tolarabilty in the Treatment of Insomnia" Adis Drug Evaluation 59(4): 865-889 (Apr. 2000).

Kansy, M. "Physiochemical High Throughput Screening: Parallel Artificial Membrane Permeation Assay in the Description of Passive Absorption Processes" Journal of Medicinal Chemstry vol. 41, No. 7: 1007-1010, (1998) .

Lader, M.H. "Implications of hypnotic flexibility on patterns of clinical use" UCP Supplement 116: 14-19 (Jan. 2001).

Merlotti, L. et al. "The Dose Effects of Zolpidem on the Sleep of Healthy Normals" J. Clinical Psychopharmacology 9(1): 9-14 (Feb. 1989).

Mitler, M.M. "Nonselective and Selective Benzodiazepine Receptor Agonists—Where Are We Today?" Sleep 23 (Supplement 1): S39-S47 (2000).

Nail, S. "Fundamentals of Freeze-Drying" Development and Manufacture of Protein Pharmaceuticals 281-360 (2002).

Rathbone, M. "The oral cavity as a site for systemic drug delivery." Advanced Drug Delivery Reviews 13: 1-22 (1994).

Scharf, M.B. "Individualizing therapy for early, middle-of-the-night and late-night insomnia" UCP Supplement 116: 20-24 (Jan. 2001).

Shangold, G. et al. "NovaDel NDA for Nitroglycerin Lingual Spray Is Accepted For Review By FDA" Khandaker Analytical Review 3(5): 28-30, (2004).

Squier, C. "Lipid Content and Water Permeability of Skin and Oral Mucosa" The Journal of Investigative Dermatology p. 123-126 (1991).

Squier, C. "Structure and Function of the Oral Mucosa and Implications for Drug Delivery" Oral Mucosa Drug Delivery p. 1-26 (1996).

Tabak, L. "Role of salivary mucins in the protection of the oral cavity" Journal of Oral Pathology 11: 1-17 (1982).

Thapa, P. "Lyophilization of Unit Dose Pharmaceutical Dosage Forms" Drug Development and Industrial Pharmacy vol. 29 No. 5: 595-602 (2003).

Walsh, J.K. et al. "Lack of Residual Sedation Following Middle-of-the-Night Zaleplon Administration in Sleep Maintenance Insomnia" Clin. Neuropharmacology 23(1): 17-21 (2000).

Wertz, F. "Cellular and Molecular Basis of Barrier Function in Oral Epithelium" Critical Reviews in Therapeutic Drug Carrier Systems 8(3): 237-269 (1991).

* cited by examiner

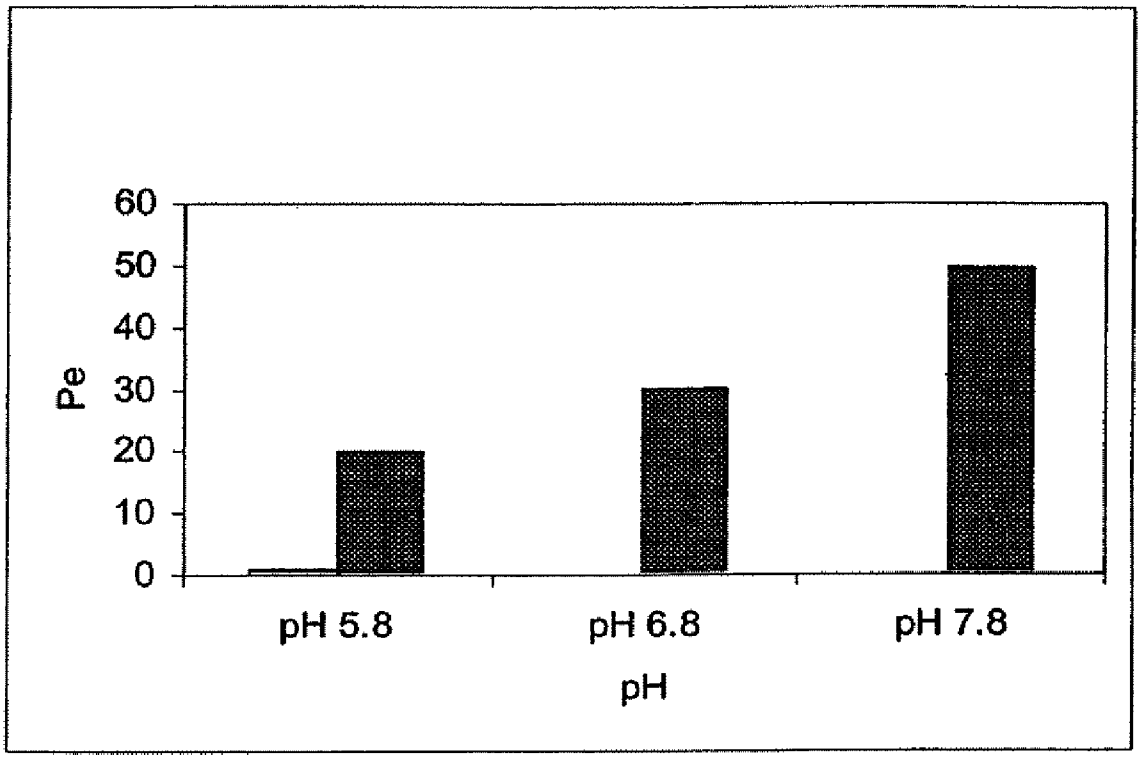


FIG. 1

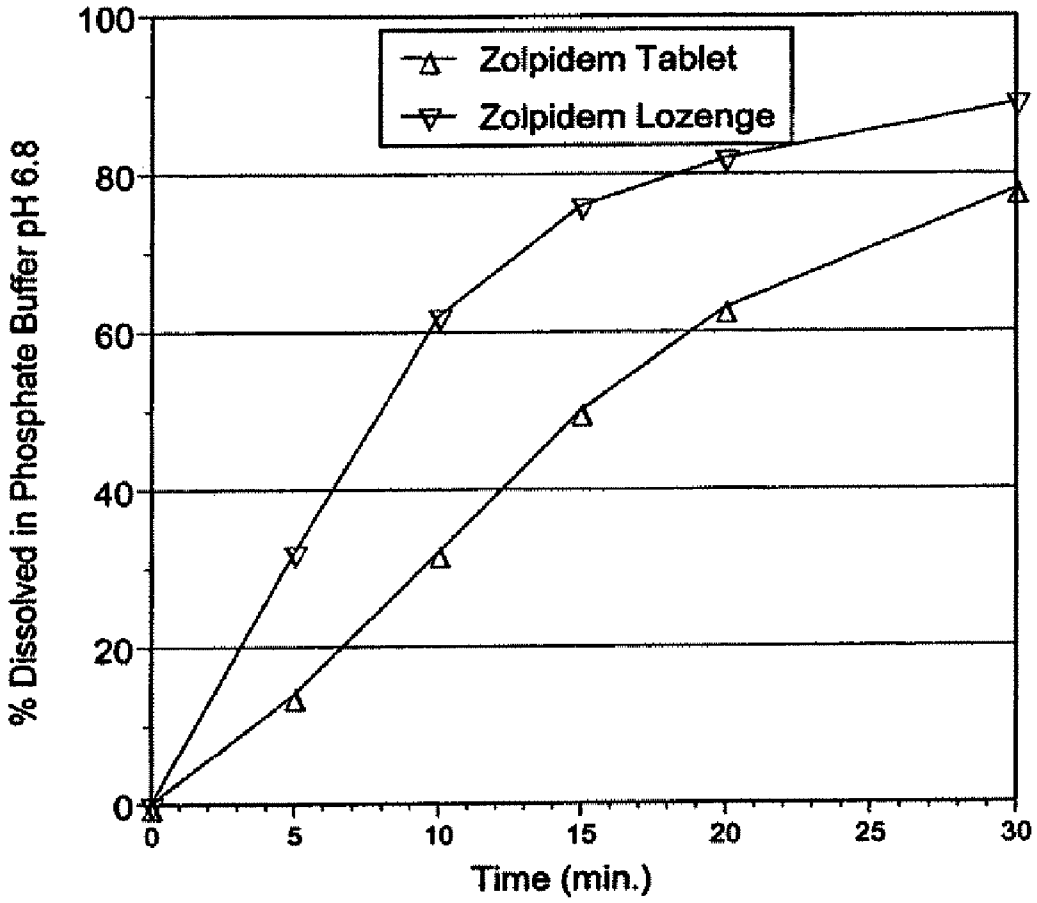

Zolpidem Tablet
Zolpidem Lozenge
% Dissolved in Phosphate Buffer pH 6.8
Time (min.)
0
20
40
60
80
100
0
5
10
15
20
25
30

FIG. 2

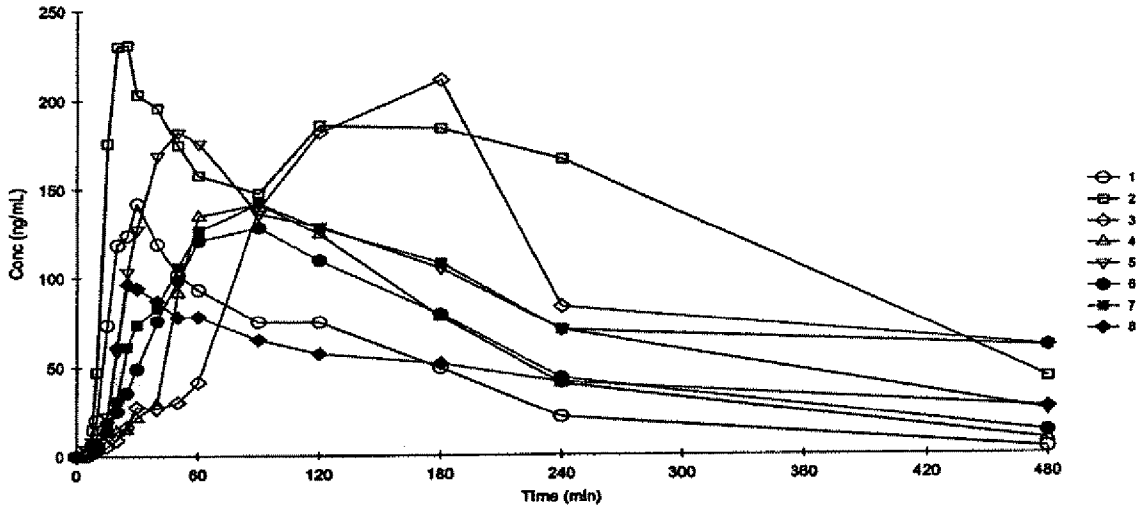

250
200
150
100
50
0
Conc (ng/mL)
0
60
120
180
240
300
360
420
480
Time (min)
1
2
3
4
5
6
7
8

FIG. 3

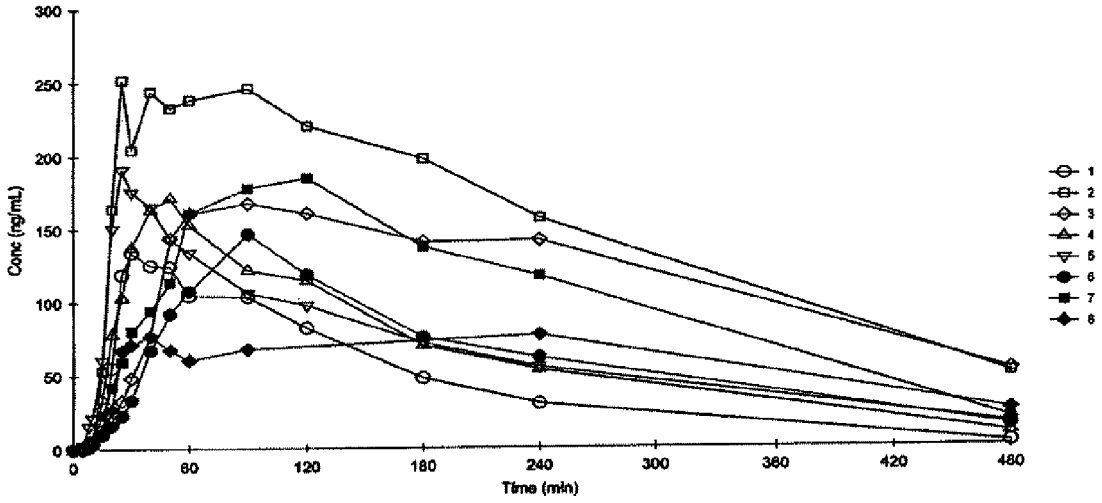

300
250
200
150
100
50
0
Conc (ng/mL)
0
60
120
180
240
300
360
420
480
Time (min)
1
2
3
4
5
6
7
8

FIG. 4

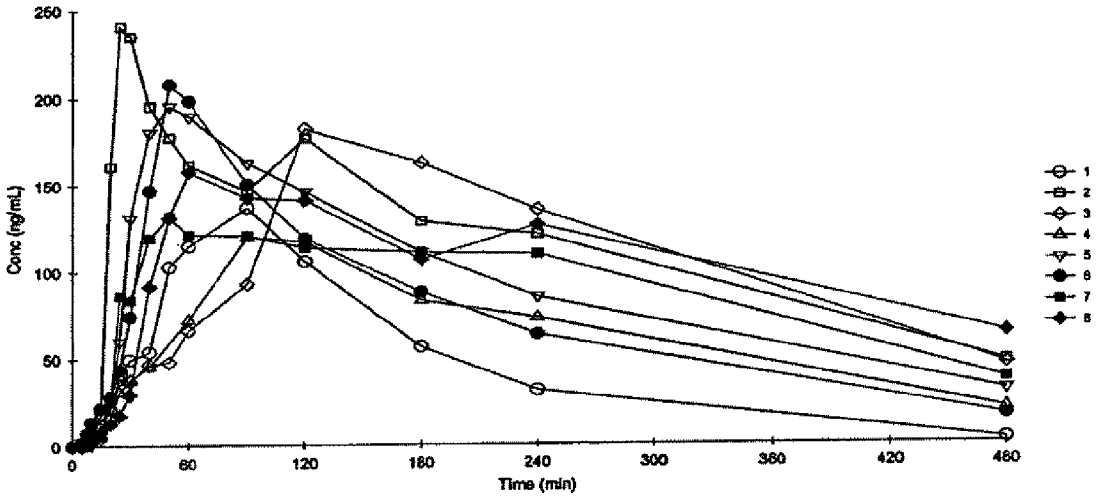

250
200
150
100
50
0
Conc (ng/mL)
0
60
120
180
240
300
360
420
480
Time (min)
1
2
3
4
5
6
7
8

FIG. 5

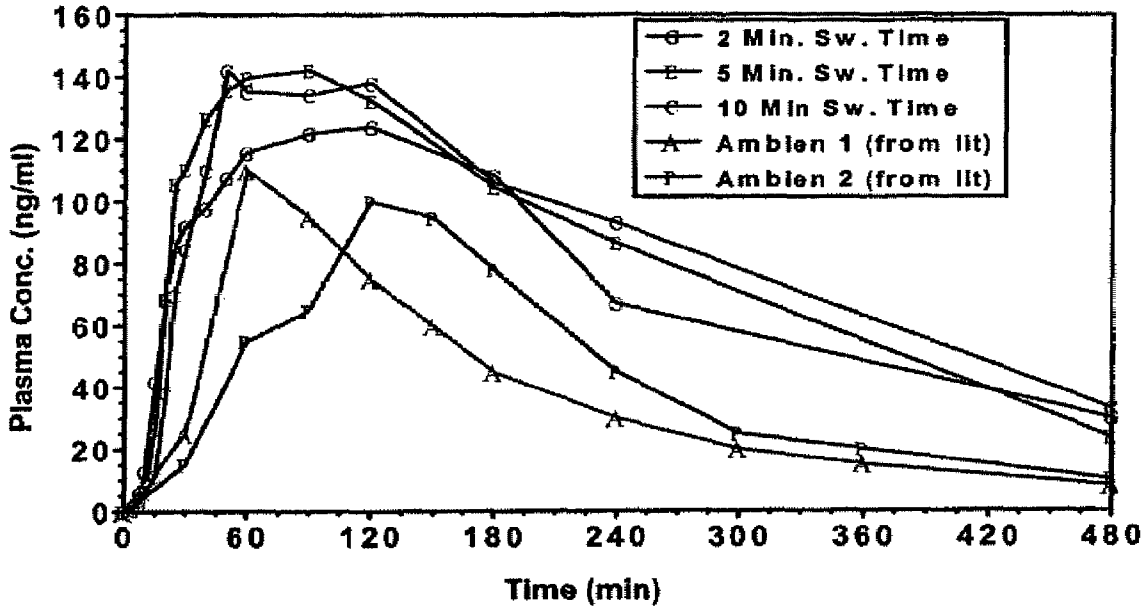

160
140
120
100
80
60
40
20
0
Plasma Conc. (ng/ml)
0
60
120
180
240
300
360
420
480
Time (min)
2 Min. Sw. Time
5 Min. Sw. Time
10 Min Sw. Time
Ambien 1 (from lit)
Ambien 2 (from lit)

FIG. 6

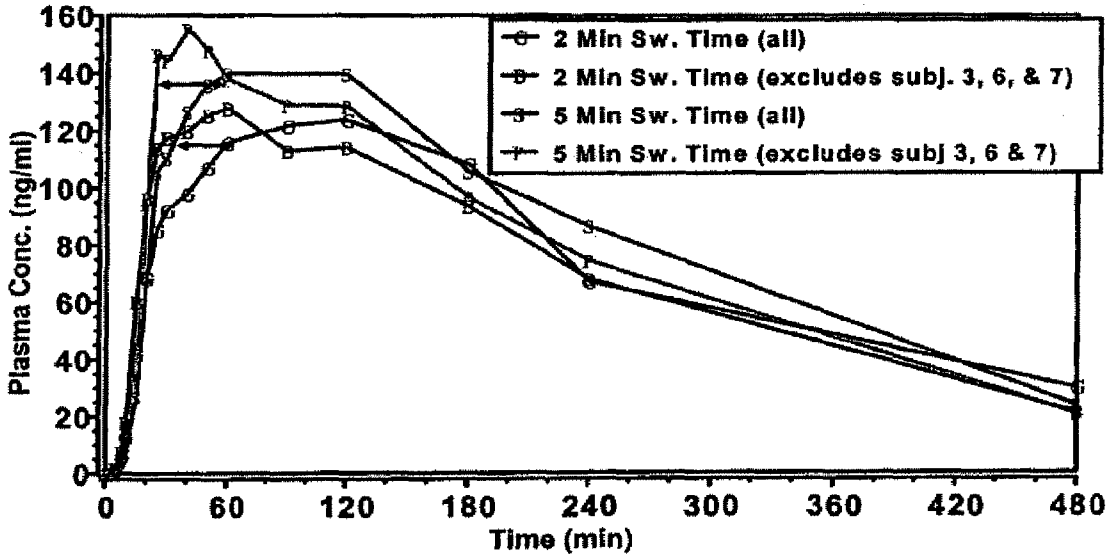

2 Min Sw. Time (all)
2 Min Sw. Time (excludes subj. 3, 6, & 7)
5 Min Sw. Time (all)
5 Min Sw. Time (excludes subj 3, 6 & 7)
Plasma Conc. (ng/ml)
160
140
120
100
80
60
40
20
0
0
60
120
180
240
300
360
420
480
Time (min)

FIG. 7

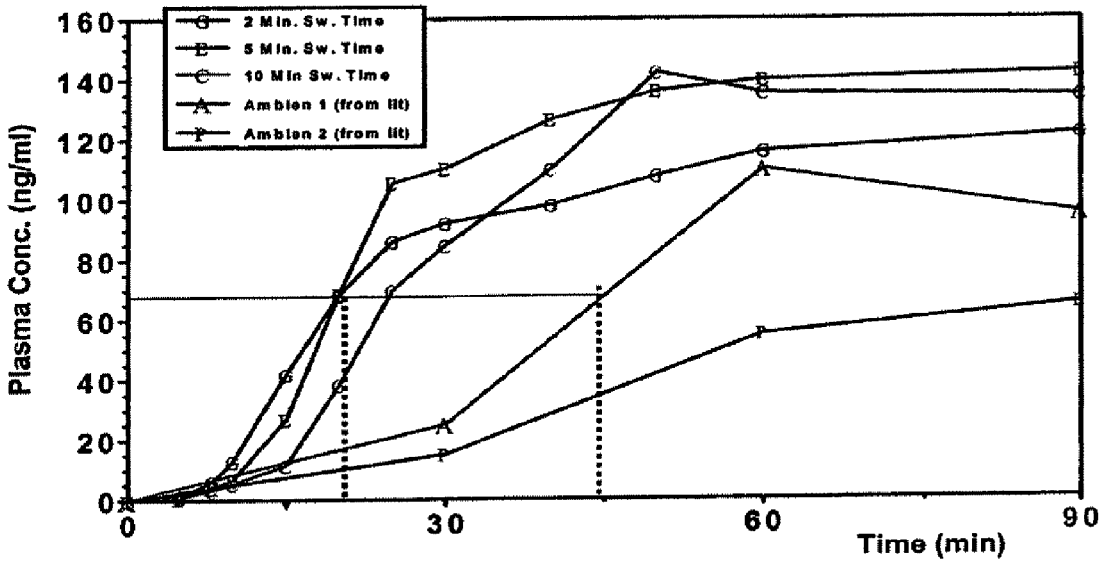

2 Min. Sw. Time
5 Min. Sw. Time
10 Min Sw. Time
Ambien 1 (from Ht)
Ambien 2 (from Ht)
Plasma Conc. (ng/ml)
160
140
120
100
80
60
40
20
0
0
30
60
90
Time (min)

FIG. 8

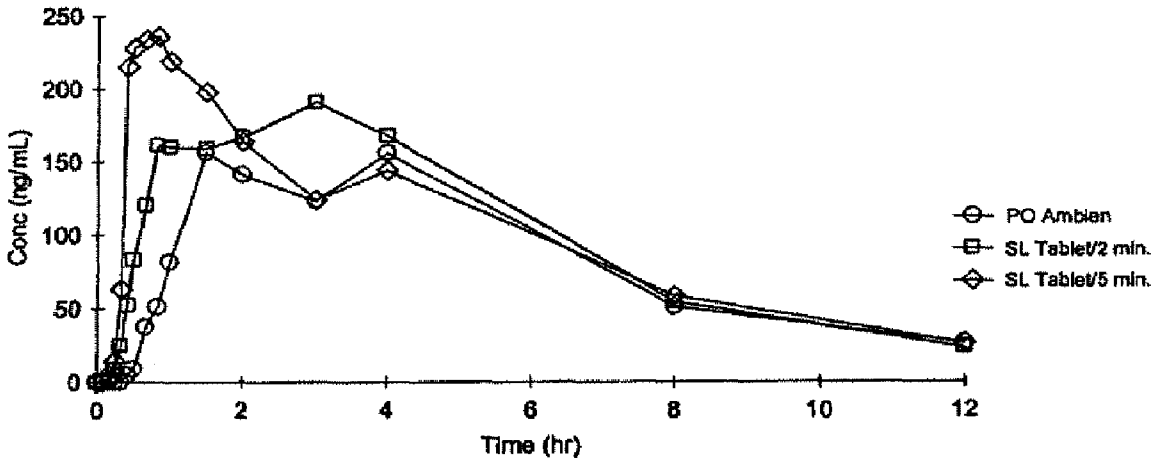

250
200
150
100
50
0
Conc (ng/mL)
0
2
4
6
8
10
12
Time (hr)
PO Ambien
SL Tablet/2 min.
SL Tablet/5 min.

FIG. 9

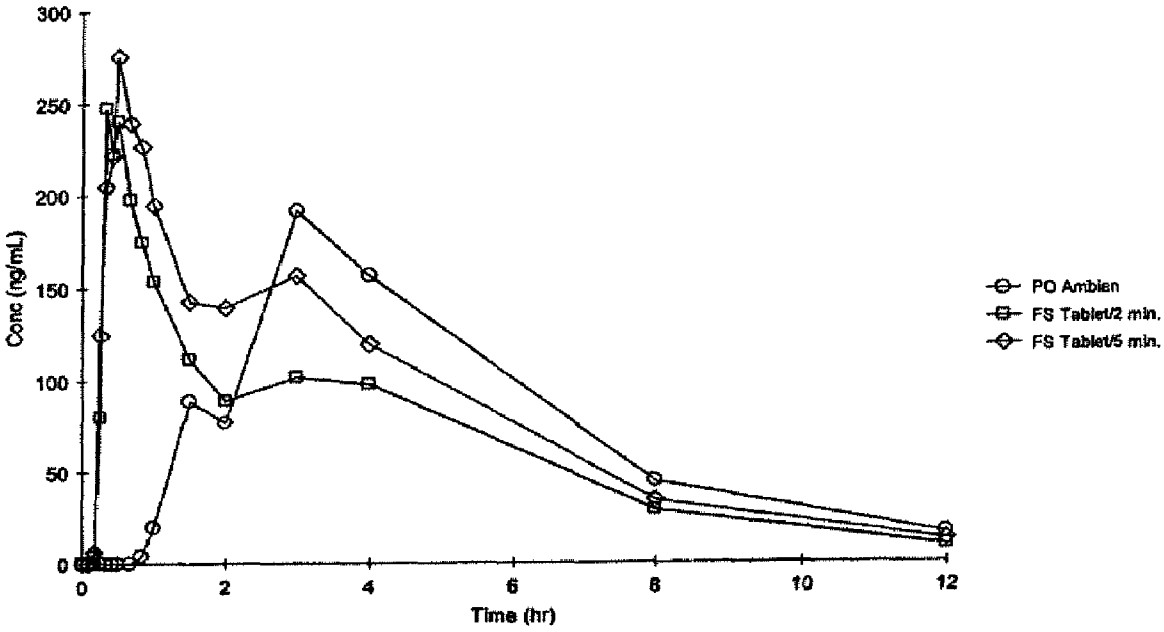

300
250
200
150
100
50
0
Conc (ng/mL)
0
2
4
6
8
10
12
Time (hr)
PO Ambien
FS Tablet/2 min.
FS Tablet/5 min.

FIG. 10

COMPOSITIONS FOR DELIVERING HYPNOTIC AGENTS ACROSS THE ORAL MUCOSA AND METHODS OF USE THEREOF

CROSS-REFERENCES TO RELATED APPLICATIONS

This is a continuation of U.S. application Ser. No. 11/060,641, filed Feb. 16, 2005, which claims priority to U.S. Provisional Application No. 60/608,957 (converted from U.S. application Ser. No. 10/783,118), filed Feb. 17, 2004, and U.S. Provisional Application No. 60/598,629, filed Aug. 3, 2004, each of which is herein incorporated by reference in its entirety for all purposes.

BACKGROUND OF THE INVENTION

Insomnia is a condition that affects a person's ability to fall asleep or to maintain sleep. It is the most common sleep disorder, affecting millions of Americans each year. Benzodiazepines, which are available as short, intermediate, or long-acting hypnotic agents, have proven useful in treating insomnia. These benzodiazepines are thought to bind non-selectively to benzodiazepine$_1$ (omega$_1$) and benzodiazepine$_2$ (omega$_2$) receptors. This non-selective binding may be responsible for some of the potential problems associated with the use of benzodiazepine compounds as hypnotics. For example, some benzodiazepines are thought to interfere with memory, cognition, and psychomotor function. In addition, problems with altered sleep architecture, rebound insomnia, hangover effects, and abuse potential have been reported with benzodiazepine use.

Selective benzodiazepine$_1$ receptor agonists have been developed and studied. For example, zolpidem (Ambien®; Searle and Co.) and zaleplon (Sonata®; Wyeth-Ayerst Co.) are non-benzodiazepine sedative agents thought to selectively bind to benzodiazepine (BZ_1) receptors. Zolpidem, an imidazopyridine, has been demonstrated to reduce sleep latency, increase sleep duration, and reduce nighttime awakenings. In addition, zolpidem has been found to preserve stage III and stage 1V sleep, and to result in less disruption of REM (Rapid Eye Movement) sleep. Zaleplon is a pyrazolopyrimidine derivative, which has also proven useful as a hypnotic agent. However, zolpidem and zaleplon are both poorly soluble in aqueous media.

Typically, these hypnotic agents are delivered as oral dosages, which are formulated, for example, as tablets or capsules that are swallowed. Oral administration, however, has several disadvantages, such as drug losses during hepatic first pass metabolism, during enzymatic degradation within the GI tract, and during absorption. These drug losses not only increase the variability in drug response, but also often require that the medicament be given in greater initial doses. In addition, because 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.

Accordingly, other routes of drug administration have been investigated, including those involving transport across the mucous membranes. Of the various mucous membranes (e.g., oral, rectal, vaginal, ocular, nasal, etc.), drug delivery via the mucous membranes in the oral cavity seems to be the most easily tolerated by patients. In addition to avoiding the problems with traditional oral administration, drug delivery via the mucous membranes of the oral cavity has certain other 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.

In addition to the differences in permeability of the various mucous membranes, the extent of drug delivery is also affected by the properties of the drug to be delivered. The ability of a molecule to pass through any mucous membrane is dependent upon its size, its lipid solubility, and the extent to which it is ionized, among other factors.

The extent to which a drug is ionized has further been investigated with respect to drug delivery across the mucous membranes. Ionization is dependent on the dissociation constant (pKa), and the pH of the molecule's surrounding environment. In its un-ionized form, a drug is sufficiently lipophilic to traverse a membrane via passive diffusion. In fact, according to the pH partition hypothesis, only un-ionized, non-polar drugs will penetrate a lipid membrane.

At equilibrium, the concentrations of the un-ionized form of the drug are equal on both sides of the membrane. As the concentration gradient drives passive diffusion, an increase in the percentage of the un-ionized form of a drug correspondingly increases the transmucosal absorption of the drug. Maximum absorption across the membrane is thought to occur when a drug is 100% in its un-ionized form. Similarly, absorption across the membrane decreases as the extent of ionization increases. Therefore, one may influence the extent of drug absorption across the mucous membranes of the oral cavity by altering the salivary pH.

Some of the known transmucosal dosage forms include the use of a single buffering agent in order to change the pH of the saliva and tissues surrounding the buccal mucosa. However, these single buffering agents typically react with an acid or a base to create a final pH that is dependent upon the initial pH of the saliva of the user. A buffering agent used to attain a final pH that is dependent upon the initial pH of the user results in great variability. The extent of ionization, and hence the extent of absorption across the mucous membranes cannot be predicted with any sort of accuracy. This may pose significant problems when calculating precise doses, minimizing variability in patient response, and proving consistency in drug loading to the regulatory authorities. In addition, a single buffering agent is typically not capable of sustaining a given pH over a period of time for optimal absorption. While others in the art have disclosed the use of more than one buffering agent, these aforementioned problems are not easily cured by the nonchalant addition of an extra buffering agent, which may be unsafe and cause irreversible damage to the mucous membranes of the oral cavity. As such, a buffering system capable of achieving and sustaining a final pH independent of the initial pH in order to increase transmucosal absorption has not heretofore been demonstrated.

Similarly, a buffer system that facilitates substantially complete conversion of the ionized form of a drug to the un-ionized form in the shortest period of time, which is criti-

cal for producing rapid delivery of practically an entire drug dose across the oral mucosa, has not heretofore been demonstrated. Previous dosage forms resulted in great variability in drug delivery, due to the variability in the rates in which a drug was released from its carrier. That is, the rates of drug release in previously described chewing gums or lozenges are largely dependent upon the rate of chewing or sucking of the user. The variability in these rates from user to user further exacerbates the ability to predict the final amount of drug that will enter systemic circulation. In addition, the rate of drug release from the carrier is further dependent upon the ability of the drug to be released therefrom. Often times, the carrier (e.g., gum base) strongly adheres to the drug, making portions of the drug unavailable for absorption.

Accordingly, there is a need in the art for compositions for delivering hypnotic agents across the oral mucosa having buffer systems that facilitate absorption of the agents in a safe and stable manner. Similarly, there is a need in the art for compositions for delivering hypnotic agents across the oral mucosa having a buffer system that produces a final pH, independent of the initial pH, and sustains that final pH for a given period of time. In addition, there is a need in the art for compositions capable of rapidly facilitating substantially complete conversion of the hypnotic agent from its ionized to its un-ionized form. The present invention satisfies these and other needs.

BRIEF SUMMARY OF THE INVENTION

The present invention provides novel compositions for the delivery of a hypnotic agent across the oral mucosa. In particular, the buffer system in the compositions of the present invention raises the pH of saliva to a pH greater than about 7.8, thereby facilitating the substantially complete conversion of the hypnotic agent from its ionized to its un-ionized form. As a result, the dose of hypnotic agent is rapidly and efficiently absorbed by the oral mucosa with surprisingly low inter-subject variability (e.g., lower variability than absorption across the gut in the same patients). Furthermore, delivery of the hypnotic agent across the oral mucosa advantageously bypasses hepatic first pass metabolism of the drug and avoids enzymatic degradation of the drug within the gastrointestinal tract. Methods for using the compositions of the present invention for treating sleep disorders such as insomnia are also provided.

As such, in one aspect, the present invention provides a solid composition for delivery of a hypnotic agent across the oral mucosa, the composition comprising:

(a) a hypnotic agent selected from the group consisting of an imidazopyridine, a dihydropyrrolopyrazine, a pyrazolopyrimidine, and a pharmaceutically acceptable salt thereof;

(b) a carrier that provides complete buccal or sublingual disintegration in about 5 minutes or less following administration to the mouth; and

(c) a binary buffer system comprising a carbonate salt and a bicarbonate salt,

wherein the binary buffer system raises the pH of saliva to a pH greater than about 7.8, irrespective of the starting pH of saliva.

In another aspect, the present invention provides a composition for delivery of a hypnotic agent across the oral mucosa, the composition comprising:

(a) a hypnotic agent selected from the group consisting of an imidazopyridine, a dihydropyrrolopyrazine, a pyrazolopyrimidine, and a pharmaceutically acceptable salt thereof;

(b) a carrier; and

(c) a binary buffer system comprising a carbonate salt and a bicarbonate salt,

wherein the binary buffer system raises the pH of saliva to a pH greater than about 7.8, irrespective of the starting pH of saliva.

In yet another aspect, the present invention provides a composition for delivery of a hypnotic agent across the oral mucosa, the composition comprising:

(a) a hypnotic agent selected from the group consisting of an imidazopyridine, a dihydropyrrolopyrazine, a pyrazolopyrimidine, and a pharmaceutically acceptable salt thereof;

(b) a carrier; and

(c) a binary buffer system comprising a carbonate salt or a bicarbonate salt and a second buffering agent,

wherein the binary buffer system raises the pH of saliva to a pH greater than about 7.8, irrespective of the starting pH of saliva.

In still yet another aspect, the present invention provides a composition for delivery of a hypnotic agent across the oral mucosa, the composition comprising:

(a) a hypnotic agent selected from the group consisting of an imidazopyridine, a dihydropyrrolopyrazine, a pyrazolopyrimidine, and a pharmaceutically acceptable salt thereof;

(b) a carrier; and

(c) a binary buffer system comprising a metal oxide and a citrate, phosphate, or borate salt,

wherein the binary buffer system raises the pH of saliva to a pH greater than about 7.8, irrespective of the starting pH of saliva.

In a further aspect, the present invention provides a composition for delivery of a hypnotic agent across the oral mucosa, the composition comprising:

(a) a hypnotic agent selected from the group consisting of an imidazopyridine, a dihydropyrrolopyrazine, a pyrazolopyrimidine, and a pharmaceutically acceptable salt thereof;

(b) a carrier; and

(c) a ternary buffer system comprising a carbonate salt, a bicarbonate salt, and a third buffering agent,

wherein the ternary buffer system raises the pH of saliva to a pH greater than about 7.8, irrespective of the starting pH of saliva.

In another aspect, the present invention provides a composition for delivery of a hypnotic agent across the oral mucosa, the composition comprising:

(a) a hypnotic agent selected from the group consisting of an imidazopyridine, a dihydropyrrolopyrazine, a pyrazolopyrimidine, and a pharmaceutically acceptable salt thereof;

(b) a carrier; and

(c) a buffer system comprising 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,

wherein the buffer system raises the pH of saliva to a pH greater than about 7.8, irrespective of the starting pH of saliva.

In yet another aspect, the present invention provides a method for treating a sleep disorder in a subject in need thereof, the method comprising:

administering to the subject a composition comprising a therapeutically effective amount of a hypnotic agent selected

from the group consisting of an imidazopyridine, a dihydropyrrolopyrazine, a pyrazolopyrimidine, and a pharmaceutically acceptable salt thereof; a carrier; and a binary buffer system comprising a carbonate salt and a bicarbonate salt, wherein the binary buffer system raises the pH of saliva to a pH greater than about 7.8, irrespective of the starting pH of saliva.

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** is a bar chart illustrating the relationship between the pH and membrane permeation for zolpidem tartrate.

FIG. **2** shows the mean dissolution profiles for a zolpidem quick-dissolving tablet and zolpidem lozenge of the present invention.

FIG. **3** shows the plasma concentration over time in each subject for Formulation A (zolpidem sublingual powdered tablet) at a 2 minute swallowing time.

FIG. **4** shows the plasma concentration over time in each subject for Formulation A at a 5 minute swallowing time.

FIG. **5** shows the plasma concentration over time in each subject for Formulation A at a 10 minute swallowing time.

FIG. **6** shows the mean plasma concentration over time for Formulation A at the 3 different swallowing times and for Formulation B (PO Ambien®), which was obtained from the literature.

FIG. **7** shows the mean plasma concentration over time for Formulation A at swallowing times of 2 and 5 minutes using the data from all subjects or excluding the data from subjects 3, 6, and 7.

FIG. **8** is an expanded view of the first 90 minutes shown in FIG. **4**.

FIG. **9** shows a representative plasma concentration over time for Formulation C(SL Tablet) at swallowing times of 2 and 5 minutes and for Formulation B.

FIG. **10** shows a representative plasma concentration over time for Formulation D (FS Tablet) at swallowing times of 2 and 5 minutes and for Formulation B.

DETAILED DESCRIPTION OF THE INVENTION

I. 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 terms "therapeutic agent" and "drug" are used interchangeably herein to refer to a substance having a pharmaceutical, pharmacological, psychosomatic, or therapeutic effect. Preferably, the therapeutic agent or drug is a hypnotic agent. Suitable hypnotic agents for use in the present invention include, without limitation, an imidazopyridine compound such as zolpidem or alpidem; a dihydropyrrolopyrazine compound such as zopeclon; a pyrazolopyrimidine compound such as zaleplon or indiplon; pharmaceutically acceptable salts thereof; and combinations thereof. In a particularly preferred embodiment, the hypnotic agent is zolpidem, in all suitable forms.

The term "therapeutically effective amount" refers to the amount of a hypnotic agent that is capable of achieving a therapeutic effect in a subject in need thereof. For example, a therapeutically effective amount of a hypnotic agent can be the amount that is capable of preventing or relieving one or more symptoms associated with a sleep disorder.

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 terms "disintegration" and "dissolution" are used interchangeably herein to refer to the reduction of a solid dosage form of the present invention to a liquid form. More particularly, a complete disintegration or dissolution 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., 5 minutes or less, after administration. Suitable methods known in the art for determining the disintegration profile of a solid dosage form include, e.g., the United States Pharmacopeia (USP) disintegration test. Suitable methods known in the art for determining the dissolution profile of a solid dosage form include, e.g., USP dissolution tests such as USP <711> Apparatus 1 or USP <711> Apparatus 2.

As used herein, the phrase "substantially complete conversion of the hypnotic agent from its ionized to its un-ionized form" refers to greater than about 50% conversion of the hypnotic agent from its ionized form into its un-ionized form. For example, the buffer system may favor at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 99% conversion of the hypnotic agent 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 compositions of the present invention have an RSD for C_{max} of about 27% 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% versus about 100% for commercial oral tablets such as Ambien® tablets.

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.

II. General

The present invention provides novel compositions for the delivery of a hypnotic agent across the oral mucosa. In particular, the buffer system in the compositions of the present invention raises the pH of saliva to a pH greater than about 7.8, thereby facilitating the substantially complete conversion of the hypnotic agent from its ionized to its un-ionized form. As a result, the dose of hypnotic agent is rapidly and efficiently absorbed by the oral mucosa with surprisingly low inter-subject variability in terms of maximum plasma concentration (C_{max}) and the time to reach the maximum plasma concentration (T_{max}). Furthermore, delivery of the hypnotic agent across the oral mucosa advantageously bypasses hepatic first pass metabolism of the drug and avoids enzymatic degradation of the drug within the gastrointestinal tract, resulting in increased bioavailability of the hypnotic agent and reduced time to onset of therapeutic activity as compared to traditional dosage forms for oral (e.g., tablet) administration. Methods for using the compositions of the present invention for treating sleep disorders such as various types of insomnia are also provided.

The present invention is based upon the surprising discovery that sublingual delivery of zolpidem compositions containing the buffer systems described herein provides both increased bioavailability of the therapeutic agent and reduced time to onset of therapeutic activity that far surpass those observed for commercial oral tablets such as Ambien® tablets and buccal tablets such as zolpidem FlashDose® tablets (Biovail Technologies Ltd.; Chantilly, Va.). In fact, it was counterintuitive to expect that the rapidly disintegrating zolpidem solid dosage forms described herein would provide the rapid absorption and marked increase in bioavailability of zolpidem that was observed. As a result, the zolpidem in the compositions of the present invention reaches the systemic circulation in a substantially shorter period of time and at a substantially higher concentration than the zolpidem in either of the commercial tablet compositions. Thus, the zolpidem compositions of the present invention are superior to the commercial tablet compositions in reducing the time to onset of therapeutic activity, maintaining sleep (e.g., total sleep time, number of awakenings), enhancing sleep quality, eliminating the effect of food, and reducing any morning-after residual effects.

III. Description of the Embodiments

In one aspect, the present invention provides a solid composition for delivery of a hypnotic agent across the oral mucosa, the composition comprising:

(a) a hypnotic agent selected from the group consisting of an imidazopyridine, a dihydropyrrolopyrazine, a pyrazolopyrimidine, and a pharmaceutically acceptable salt thereof;

(b) a carrier that provides complete buccal or sublingual disintegration in about 5 minutes or less following administration to the mouth; and

(c) a binary buffer system comprising a carbonate salt and a bicarbonate salt,

wherein the binary buffer system raises the pH of saliva to a pH greater than about 7.8, irrespective of the starting pH of saliva.

In certain instances, the binary buffer system raises the pH of saliva to a pH greater than about 8.5, irrespective of the starting pH of saliva. In certain other instances, the binary buffer system raises the pH of saliva to a pH greater than about 9 (e.g., about 9-11), irrespective of the starting pH of saliva. In one embodiment, the imidazopyridine hypnotic agent is selected from the group consisting of zolpidem and alpidem. Preferably, the imidazopyridine hypnotic agent is zolpidem. Any form of zolpidem is suitable for use in the compositions described herein, e.g., a salt form of zolpidem (e.g., zolpidem tartrate), a free base form of zolpidem, or a mixture thereof. In another embodiment, the dihydropyrrolopyrazine hypnotic agent is zopeclon. In yet another embodiment, the pyrazolopyrimidine hypnotic agent is selected from the group consisting of zaleplon and indiplon.

In certain instances, the carrier provides complete buccal or sublingual disintegration in about 2 minutes or less following administration. In certain other instances, the carrier comprises at least one binder and at least one disintegrating agent in such relative proportion to provide a buccal or sublingual disintegration 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 another embodiment, the carbonate salt is selected from the group consisting of sodium carbonate, potassium carbonate, calcium carbonate, ammonium carbonate, and magnesium carbonate. In yet another embodiment, the bicarbonate salt is 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.

In yet another embodiment, the compositions of the present invention are in a dosage form selected from the group consisting of 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 composition is a lozenge or a dissolving tablet. A description of lozenge, chewing gum, chewable tablet, slow-dissolving tablet, and quick-dissolving tablet compositions containing a hypnotic agent is provided in the Examples below.

In a preferred embodiment, the hypnotic agent 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 hypnotic agent is delivered across the sublingual mucosa.

In another embodiment, the carrier is selected from the group consisting of a binder, a gum base, and combinations thereof. Suitable binders for use in the compositions of the present invention include, without limitation, sugar alcohols

such as mannitol, sorbitol, and xylitol; sugars such as lactose, dextrose, sucrose, glucose, and powdered sugar; natural gums such as acacia gum, xanthan gum, guar gum, tara gum, mesquite gum, fenugreek gum, locust bean gum, ghatti gum, and tragacanth gum; other substances such as inositol, molasses, maltodextrin, starch, cellulose, microcrystalline cellulose, polyvinylpyrrolidone, alginate, extract of Irish moss, panwar gum, mucilage of isapol husks, Veegum®, larch arabogalactan, gelatin, methylcellulose, ethylcellulose, carboxymethylcellulose, hydroxypropylmethylcellulose, polyacrylic acid (e.g., Carbopol), calcium silicate, calcium phosphate, dicalcium phosphate, calcium sulfate, kaolin, sodium chloride, polyethylene glycol; and combinations thereof. Suitable gum bases for use in the compositions of the present invention include, for example, materials selected from among the many water-insoluble and saliva-insoluble gum base materials known in the art. In certain 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).

In yet another embodiment, the compositions of the present invention can further comprise a sweetening agent, a flavoring agent, a protecting agent, a plasticizer, a wax, an elastomeric solvent, a filler material, a preservative, or combinations thereof. In still yet another embodiment, the compositions of the present invention can further comprise a lubricating agent, a wetting agent, an emulsifying agent, a solubilizing agent, a suspending agent, a coloring agent, a disintegrating agent, or combinations thereof. 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.).

In preferred embodiments of the present invention, the hypnotic agent is zolpidem and the binary buffer system comprises 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 other preferred embodiments, 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 certain instances, the composition comprises from about 1.0 to about 5.5 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 4.5 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 candies 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 1.0 to about 5.0 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 4.0 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.

In another aspect, the present invention provides a composition for delivery of a hypnotic agent across the oral mucosa, the composition comprising:

(a) a hypnotic agent selected from the group consisting of an imidazopyridine, a dihydropyrrolopyrazine, a pyrazolopyrimidine, and a pharmaceutically acceptable salt thereof;

(b) a carrier; and

(c) a binary buffer system comprising a carbonate salt and a bicarbonate salt,

wherein the binary buffer system raises the pH of saliva to a pH greater than about 7.8, irrespective of the starting pH of saliva.

In certain instances, the binary buffer system raises the pH of saliva to a pH greater than about 8.5, irrespective of the starting pH of saliva. In certain other instances, the binary buffer system raises the pH of saliva to a pH greater than about 9 (e.g., about 9-11), irrespective of the starting pH of saliva. Suitable imidazopyridine, dihydropyrrolopyrazine, and pyrazolopyrimidine hypnotic agents for use in the present invention are described above. Suitable carbonate salts and bicarbonate salts for use in the binary buffer systems of the present invention are also described above.

In another embodiment, the compositions of the present invention are in any of the dosage forms described above. Preferably, the hypnotic agent is delivered across an oral mucosa as described above. In yet another embodiment, the carrier is selected from the group consisting of a binder, a gum base, and combinations thereof. Suitable binders and gum bases for use in the compositions of the present invention are described above. In certain instances, the carrier provides a buccal or sublingual disintegration time of about 10 minutes or less, preferably about 5 minutes or less, and more preferably about 2 minutes or less, following administration. In certain other instances, the carrier comprises at least one binder and at least one disintegrating agent in such relative proportion to provide a buccal or sublingual disintegration time of about 10 minutes or less, preferably about 5 minutes or less, and more preferably about 2 minutes or less, following administration.

In yet another embodiment, the compositions of the present invention can further comprise one or more of the additional agents described above. In preferred embodiments, the average particle size of the drug in the compositions described herein is about 20 microns and/or is less than or equal to the average particle size of the carrier ingredients (e.g., gum base, binders, etc.).

In other preferred embodiments of the present invention, the hypnotic agent is zolpidem and the binary buffer system comprises sodium carbonate and sodium bicarbonate. Preferred amounts of each of these components is described above, along with preferred dosage forms and their preferred weight.

In yet another aspect, the present invention provides a composition for delivery of a hypnotic agent across the oral mucosa, the composition comprising:

(a) a hypnotic agent selected from the group consisting of an imidazopyridine, a dihydropyrrolopyrazine, a pyrazolopyrimidine, and a pharmaceutically acceptable salt thereof;

(b) a carrier; and

(c) a binary buffer system comprising a carbonate salt or a bicarbonate salt and a second buffering agent,

wherein the binary buffer system raises the pH of saliva to a pH greater than about 7.8, irrespective of the starting pH of saliva.

In certain instances, the binary buffer system raises the pH of saliva to a pH greater than about 8.5, irrespective of the starting pH of saliva. In certain other instances, the binary buffer system raises the pH of saliva to a pH greater than about 9 (e.g., about 9-11), irrespective of the starting pH of saliva. Suitable imidazopyridine, dihydropyrrolopyrazine, and pyrazolopyrimidine hypnotic agents for use in the present invention are described above. Suitable carbonate salts and bicarbonate salts for use in the binary buffer systems of the present invention are also described above.

In one embodiment, the second buffering agent is selected from the group consisting of a metal oxide, a citrate salt, a phosphate salt, a borate salt, an ascorbate salt, an acetate salt, and alkaline starch. Suitable metal oxides include, without limitation, magnesium oxide and aluminum oxide. Preferably, the magnesium oxide is amorphous magnesium oxide. Suitable citrate, phosphate, and borate salts include, without limitation, any salt of citric acid, phosphoric acid, or boric acid known in the art. For example, in some embodiments, the citrate salt is selected from the group consisting of sodium citrate, potassium citrate, calcium citrate, magnesium citrate, and ammonium citrate. In other embodiments, the phosphate salt is selected from the group consisting of monobasic sodium phosphate, dibasic sodium phosphate, monobasic potassium phosphate, dibasic potassium phosphate, monobasic calcium phosphate, dibasic calcium phosphate, monobasic magnesium phosphate, dibasic magnesium phosphate, monobasic ammonium phosphate, and dibasic ammonium phosphate. In yet other embodiments, the borate salt is selected from the group consisting of sodium borate, potassium borate, calcium borate, magnesium borate, and ammonium borate. In certain instances, the binary buffer system comprises a carbonate salt and a metal oxide, a citrate salt, a phosphate salt, or a borate salt. In certain other instances, the binary buffer system comprises a bicarbonate salt and a metal oxide, a citrate salt, a phosphate salt, or a borate salt.

In another embodiment, the compositions of the present invention are in any of the dosage forms described above. Preferably, the hypnotic agent is delivered across an oral mucosa as described above. In yet another embodiment, the carrier is selected from the group consisting of a binder, a gum base, and combinations thereof. Suitable binders and gum bases for use in the compositions of the present invention are described above. In certain instances, the carrier provides a buccal or sublingual disintegration time as described above. In certain other instances, the carrier comprises at least one binder and at least one disintegrating agent as described above.

In yet another embodiment, the compositions of the present invention can further comprise one or more of the additional agents described above. In preferred embodiments, the average particle size of the drug in the compositions described herein is about 20 microns and/or is less than or equal to the average particle size of the carrier ingredients (e.g. gum base, binders, etc.).

In preferred embodiments of the present invention, the hypnotic agent is zolpidem and the binary buffer system comprises sodium carbonate or sodium bicarbonate and a second buffering agent. Such compositions are preferably formulated in the form of a lozenge, candy, or dissolving tablet for sublingual administration.

In still yet another aspect, the present invention provides a composition for delivery of a hypnotic agent across the oral mucosa, the composition comprising:

(a) a hypnotic agent selected from the group consisting of an imidazopyridine, a dihydropyrrolopyrazine, a pyrazolopyrimidine, and a pharmaceutically acceptable salt thereof;

(b) a carrier; and

(c) a binary buffer system comprising a metal oxide and a citrate, phosphate, or borate salt,

wherein the binary buffer system raises the pH of saliva to a pH greater than about 7.8, irrespective of the starting pH of saliva.

In certain instances, the binary buffer system raises the pH of saliva to a pH greater than about 8.5, irrespective of the starting pH of saliva. In certain other instances, the binary buffer system raises the pH of saliva to a pH greater than about 9 (e.g., about 9-11), irrespective of the starting pH of saliva. Suitable imidazopyridine, dihydropyrrolopyrazine, and pyrazolopyrimidine hypnotic agents for use in the present invention are described above.

Suitable metal oxides include, without limitation, magnesium oxide and aluminum oxide. Suitable citrate, phosphate, and borate salts include, without limitation, any salt of citric acid, phosphoric acid, or boric acid known in the art such as those described above. In certain instances, the binary buffer system comprises a metal oxide and a citrate salt. In certain other instances, the binary buffer system comprises a metal oxide and a phosphate salt. In further instances, the binary buffer system comprises a metal oxide and a borate salt.

In one embodiment, the compositions of the present invention are in any of the dosage forms described above. Preferably, the hypnotic agent is delivered across an oral mucosa as described above. In yet another embodiment, the carrier is selected from the group consisting of a binder, a gum base, and combinations thereof. Suitable binders and gum bases for use in the compositions of the present invention are described above. In certain instances, the carrier provides a buccal or sublingual disintegration time as described above. In certain other instances, the carrier comprises at least one binder and at least one disintegrating agent as described above.

In another embodiment, the compositions of the present invention can further comprise one or more of the additional agents described above. In preferred embodiments, the average particle size of the drug in the compositions described

herein is about 20 microns and/or is less than or equal to the average particle size of the carrier ingredients (e.g., gum base, binders, etc.).

In preferred embodiments of the present invention, the hypnotic agent is zolpidem and the binary buffer system comprises amorphous magnesium oxide and a citrate, phosphate, or borate salt. Such compositions are preferably formulated in the form of a lozenge, candy, or dissolving tablet for sublingual administration.

In a further aspect, the present invention provides a composition for delivery of a hypnotic agent across the oral mucosa, the composition comprising:

(a) a hypnotic agent selected from the group consisting of an imidazopyridine, a dihydropyrrolopyrazine, a pyrazolopyrimidine, and a pharmaceutically acceptable salt thereof;

(b) a carrier; and

(c) a ternary buffer system comprising a carbonate salt, a bicarbonate salt, and a third buffering agent,

wherein the ternary buffer system raises the pH of saliva to a pH greater than about 7.8, irrespective of the starting pH of saliva.

In certain instances, the binary buffer system raises the pH of saliva to a pH greater than about 8.5, irrespective of the starting pH of saliva. In certain other instances, the binary buffer system raises the pH of saliva to a pH greater than about 9 (e.g., about 9-11), irrespective of the starting pH of saliva. Suitable imidazopyridine, dihydropyrrolopyrazine, and pyrazolopyrimidine hypnotic agents for use in the present invention are described above. Suitable carbonate salts and bicarbonate salts for use in the ternary buffer systems of the present invention are also described above.

In one embodiment, the third buffering agent is selected from the group consisting of a metal oxide, a citrate salt, a phosphate salt, a borate salt, an ascorbate salt, an acetate salt, and alkaline starch. Suitable metal oxides include, without limitation, magnesium oxide and aluminum oxide. Suitable citrate, phosphate, and borate salts include, without limitation, any salt of citric acid, phosphoric acid, or boric acid known in the art such as those described above. In certain instances, the ternary buffer system comprises a carbonate salt, a bicarbonate salt, and a metal oxide. In certain other instances, the ternary buffer system comprises a carbonate salt, a bicarbonate salt, and a citrate, phosphate, or borate salt.

In another embodiment, the compositions of the present invention are in any of the dosage forms described above. Preferably, the hypnotic agent is delivered across an oral mucosa as described above. In yet another embodiment, the carrier is selected from the group consisting of a binder, a gum base, and combinations thereof. Suitable binders and gum bases for use in the compositions of the present invention are described above. In certain instances, the carrier provides a buccal or sublingual disintegration time as described above. In certain other instances, the carrier comprises at least one binder and at least one disintegrating agent as described above.

In yet another embodiment, the compositions of the present invention can further comprise one or more of the additional agents described above. In preferred embodiments, the average particle size of the drug in the compositions described herein is about 20 microns and/or is less than or equal to the average particle size of the carrier ingredients (e.g., gum base, binders, etc.).

In preferred embodiments of the present invention, the hypnotic agent is zolpidem and the ternary buffer system comprises sodium carbonate, sodium bicarbonate, and a third buffering agent. Such compositions are preferably formulated in the form of a lozenge, candy, or dissolving tablet for sublingual administration. In instances where the third buffering agent is a metal oxide, a weight percent of the metal oxide that is greater than the combined weight percent of sodium carbonate and sodium bicarbonate is preferred.

In another aspect, the present invention provides a composition for delivery of a hypnotic agent across the oral mucosa, the composition comprising:

(a) a hypnotic agent selected from the group consisting of an imidazopyridine, a dihydropyrrolopyrazine, a pyrazolopyrimidine, and a pharmaceutically acceptable salt thereof;

(b) a carrier; and

(c) a buffer system comprising 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,

wherein the buffer system raises the pH of saliva to a pH greater than about 7.8, irrespective of the starting pH of saliva.

In certain instances, the binary buffer system raises the pH of saliva to a pH greater than about 8.5, irrespective of the starting pH of saliva. In certain other instances, the binary buffer system raises the pH of saliva to a pH greater than about 9 (e.g., about 9-11), irrespective of the starting pH of saliva. Suitable imidazopyridine, dihydropyrrolopyrazine, and pyrazolopyrimidine hypnotic agents for use in the present invention are described above. Suitable carbonate salts and bicarbonate salts for use in the buffer systems of the present invention are also described above.

Suitable metal oxides include, without limitation, magnesium oxide and aluminum oxide. Suitable citrate, phosphate, and borate salts include, without limitation, any salt of citric acid, phosphoric acid, or boric acid known in the art such as those described above. In certain instances, the buffer system comprises a carbonate salt or a bicarbonate salt, a metal oxide, and a citrate, phosphate, or borate salt. In certain other instances, the buffer system comprises a carbonate salt or a bicarbonate salt, a citrate salt, and a phosphate salt. In certain instances, the buffer system comprises a carbonate salt or a bicarbonate salt, a citrate salt, and a borate salt. In certain other instances, the buffer system comprises a carbonate salt or a bicarbonate salt, a phosphate salt, and a borate salt.

In one embodiment, the compositions of the present invention are in any of the dosage forms described above. Preferably, the hypnotic agent is delivered across an oral mucosa as described above. In yet another embodiment, the carrier is selected from the group consisting of a binder, a gum base, and combinations thereof. Suitable binders and gum bases for use in the compositions of the present invention are described above. In certain instances, the carrier provides a buccal or sublingual disintegration time as described above. In certain other instances, the carrier comprises at least one binder and at least one disintegrating agent as described above.

In another embodiment, the compositions of the present invention can further comprise one or more of the additional agents described above. In preferred embodiments, the average particle size of the drug in the compositions described herein is about 20 microns and/or is less than or equal to the average particle size of the carrier ingredients (e.g., gum base, binders, etc.).

In preferred embodiments of the present invention, the hypnotic agent is zolpidem and the buffer system comprises sodium carbonate or sodium bicarbonate 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. Such

compositions are preferably formulated in the form of a lozenge, candy, or dissolving tablet for sublingual administration.

In yet another aspect, the present invention provides a method for treating a sleep disorder in a subject in need thereof, the method comprising:

administering to the subject a composition comprising a therapeutically effective amount of a hypnotic agent selected from the group consisting of an imidazopyridine, a dihydropyrrolopyrazine, a pyrazolopyrimidine, and a pharmaceutically acceptable salt thereof; a carrier; and a binary buffer system comprising a carbonate salt and a bicarbonate salt, wherein the binary buffer system raises the pH of saliva to a pH greater than about 7.8, irrespective of the starting pH of saliva.

In a preferred embodiment, the composition delivers the hypnotic agent across the oral mucosa such as, for example, the sublingual mucosa, the buccal mucosa, or a combination thereof. In a particularly preferred embodiment, the composition is administered sublingually so that the hypnotic agent is delivered across the sublingual mucosa. Suitable sleep disorders that can be treated with the compositions of the present invention include, without limitation, insomnia such as transient insomnia, short-term insomnia, and chronic insomnia.

In certain instances, the binary buffer system raises the pH of saliva to a pH greater than about 8.5, irrespective of the starting pH of saliva. In certain other instances, the binary buffer system raises the pH of saliva to a pH greater than about 9 (e.g., about 9-11), irrespective of the starting pH of saliva. Suitable imidazopyridine, dihydropyrrolopyrazine, and pyrazolopyrimidine hypnotic agents for use in the present invention are described above. Suitable carbonate salts and bicarbonate salts for use in the binary buffer systems of the present invention are also described above.

In addition to a binary buffer system comprising a carbonate salt and a bicarbonate salt, other buffer systems are suitable for use in the compositions of the present invention. For example, in an alternative embodiment, the binary 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 binary 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 one embodiment, the compositions of the present invention are in any of the dosage forms described above. Preferably, the hypnotic agent is delivered across an oral mucosa as described above. In yet another embodiment, the carrier is selected from the group consisting of a binder, a gum base, and combinations thereof. Suitable binders and gum bases for use in the compositions of the present invention are described above. In certain instances, the carrier provides a buccal or sublingual disintegration time as described above. In certain other instances, the carrier comprises at least one binder and at least one disintegrating agent as described above.

In another embodiment, the compositions of the present invention can further comprise one or more of the additional agents described above. In preferred embodiments, the average particle size of the drug in the compositions described herein is about 20 microns and/or is less than or equal to the average particle size of the carrier ingredients (e.g., gum base, binders, etc.).

In preferred embodiments of the present invention, the hypnotic agent is zolpidem and the binary buffer system comprises sodium carbonate and sodium bicarbonate. Preferred amounts of each of these components is described above, along with preferred dosage forms and their preferred weight.

A. Hypnotic Agents

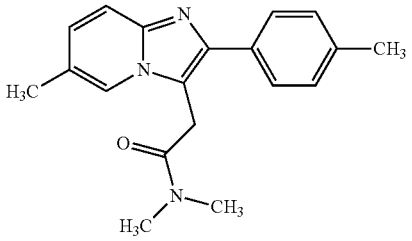
The hypnotic agents of the present invention are preferably selected from an imidazopyridine compound such as zolpidem or alpidem; a dihydropyrrolopyrazine compound such as zopeclon; a pyrazolopyrimidine compound such as zaleplon or indiplon; pharmaceutically acceptable salts thereof; and combinations thereof. More preferably, the hypnotic agent is zolpidem, in all suitable forms.

In general, the hypnotic agents of the present invention are basic compounds having an ionized form and an un-ionized form. In certain instances, the hypnotic agent is initially present at least partly in an ionized form. In certain other instances, the hypnotic agent is initially present in an un-ionized form. As described in more detail below, the buffer system of the compositions described herein helps to convert substantially all of the hypnotic agent from its ionized form to its un-ionized form. Alternatively, the buffer system helps ensure that the hypnotic agent, initially in an un-ionized form, remains in an un-ionized form.

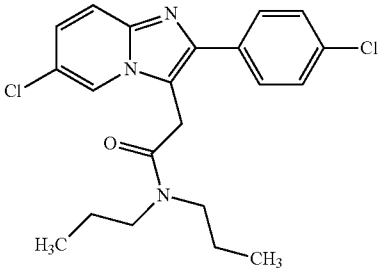
As used herein, the term "hypnotic agent" includes all pharmaceutically acceptable forms of the hypnotic agent being described. For example, the hypnotic agent can be in a racemic or isomeric mixture, a solid complex bound to an ion exchange resin, or the like. In addition, the hypnotic agent can be in a solvated form. The term "hypnotic agent" is also intended to include all pharmaceutically acceptable salts, derivatives, and analogs of the hypnotic agent being described, as well as combinations thereof. For example, the pharmaceutically acceptable salts of the hypnotic agent include, without limitation, the tartrate, succinate, tartarate, bitartarate, dihydrochloride, salicylate, hemisuccinate, citrate, maleate, hydrochloride, carbamate, sulfate, nitrate, and benzoate salt forms thereof, as well as combinations thereof and the like. Any form of the hypnotic agent is suitable for use in the compositions of the present invention, e.g., a pharmaceutically acceptable salt of the hypnotic agent (e.g., zolpidem tartrate), a free base of the hypnotic agent, or a mixture thereof.

Conversion of the ionized form to the un-ionized form for the hypnotic agent is related to pH according to the formula: $pH=pKa+Log_{10}$ (un-ionized concentration/ionized concentration). When the pH is the same as the pKa, equimolar concentrations of the un-ionized form and ionized form exist. For basic compounds such as the hypnotic agents described herein, when the pH is one unit higher than the pKa, the ratio of the un-ionized form to the ionized form is 91:9. Similarly, when the pH is two units higher than the pKa, the ratio of un-ionized form to the ionized form is 100:1. As noted above, the un-ionized form is lipophilic and, therefore, more capable of passing through mucous membranes such as the oral mucosa than the ionized form, which is lipophobic in nature. Accordingly, increasing the pH of the saliva favors conversion of the ionized form into the un-ionized form for basic compounds such as the hypnotic agents described herein, and the final pH can be determined by making use of the above formula.

The hypnotic agents of the present invention are selected from the class of compounds in the imidazopyridine, dihydropyrrolopyrazine, or pyrazolopyrimidine family and are useful in the treatment of conditions such as sleep disorders. Illustrative examples of suitable imidazopyridine compounds for use in the present invention are zolpidem, alpidem, pharmaceutically acceptable salts thereof, analogs thereof, and derivatives thereof. These imidazopyridine compounds each have an imidazopyridine group, as shown below:



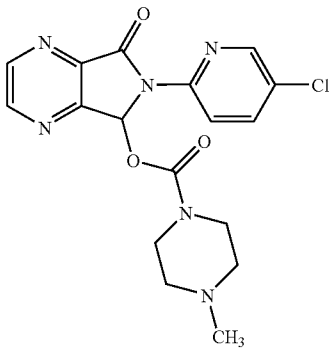
Zolpidem



Alpidem

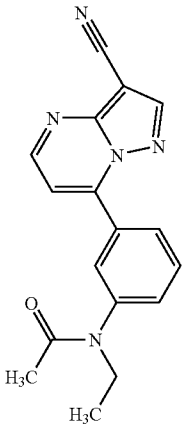
For the imidazopyridine compounds, the nitrogen in the imidazole portion of the bicyclic ring of the structure controls the extent of ionization and the degree of lipophilicity in any given medium. Typically the nitrogen in the imidazole portion imparts a pKa of from about 6.8 to about 7.5 to the molecule. Therefore, using the above formula, it can be demonstrated that about 90% conversion to an un-ionized form can be achieved for these compounds at a pH of from about 7.8 to about 8.5.

Illustrative examples of suitable dihydropyrrolopyrazine compounds for use in the present invention are zopeclon, pharmaceutically acceptable salts thereof, analogs thereof, and derivatives thereof. These dihydropyrrolopyrazines each have a dihydropyrrolopyrazine group, as shown below:

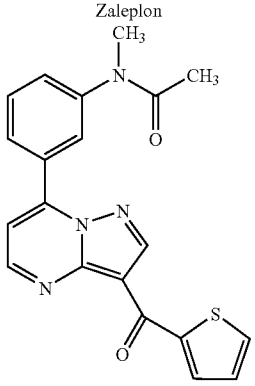


Zopeclon

Illustrative examples of suitable pyrazolopyrimidine compounds for use in the present invention are zaleplon, indiplon, pharmaceutically acceptable salts thereof, analogs thereof, and derivatives thereof. These pyrazolopyrimidines each have a pyrazolopyrimidine group, as shown below:



Zaleplon



Indiplon

For the pyrazolopyrimidine compounds, the nitrogen in the pyrimidine group controls the extent of ionization and the degree of lipophilicity in any given medium. Typically, the nitrogen in the pyrimidine group imparts a pKa of from about 8 to about 9 to the molecule. Therefore, using the above formula, it can be demonstrated that about 90% conversion to an un-ionized form can be achieved for these compounds at a pH of from about 9 to about 10.

In general, the hypnotic agents of the present invention acts as benzodiazepine receptor agonists. Preferably, the hypnotic agents selectively bind to the benzodiazepine$_1$ receptor. Without being bound to any particular theory, the therapeutic activity of the hypnotic agents of the present invention in treating sleep disorders is attributed to an enhancement of the inhibitory action of gamma-aminobutyric acid (GABA) in the central nervous system.

B. Buffer Systems

The buffer systems of the compositions described herein are capable of raising the pH of saliva to a pH greater than about 7.8, irrespective of the starting pH of saliva. In this way, the buffer system helps convert substantially all of the hypnotic agent from its ionized form to its un-ionized form. Alternatively, the buffer system helps ensure that the hypnotic agent, initially in an un-ionized form, remains in an un-ionized form. Although basic buffering agents are typically used in the buffer systems of the present invention, one skilled in

the art will appreciate that acidic agents can also be used to adjust the pH of the buffer system as long as the buffer system as a whole raises the pH of saliva to a pH greater than about 7.8.

In one embodiment, the present invention provides binary buffer systems comprising a carbonate salt and a bicarbonate salt. 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 easily determined in just a few trials. 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 1:3 to about 3:1, and still more preferably from about 1:2 to about 2:1.

The carbonate salt is generally selected from sodium carbonate, potassium carbonate, calcium carbonate, ammonium carbonate, and magnesium carbonate. Preferably, the carbonate salt is sodium carbonate or potassium carbonate. Most preferably, the carbonate salt is sodium carbonate. Similarly, the bicarbonate salt is generally selected from sodium bicarbonate, potassium bicarbonate, calcium bicarbonate, ammonium bicarbonate, and magnesium bicarbonate. Preferably, the bicarbonate salt is sodium bicarbonate or potassium bicarbonate. Most preferably, the bicarbonate salt is sodium bicarbonate. In some embodiments, a dessicant-coated sodium bicarbonate is preferred. The amount of carbonate salt and bicarbonate salt used in the binary buffer system is an amount that is sufficient to raise salivary pH to a pH of about 7.8 or more, preferably about 8.5 or more, and more preferably about 9 or more (e.g., about 9-11), irrespective of the starting pH.

In certain instances, 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 certain other instances, the combined amount of carbonate salt and bicarbonate salt is greater than or equal to the amount of the hypnotic agent, and the weight ratio of carbonate salt and bicarbonate salt to hypnotic agent 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 the hypnotic agent, and the weight ratio of carbonate salt and bicarbonate salt to hypnotic agent 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 view of the above, the buffer systems of the present invention, in some of the most preferred embodiments, are binary buffer systems containing sodium carbonate and sodium bicarbonate.

Alternatively, in another embodiment, the buffer systems of the present invention are binary buffer systems comprising a carbonate salt or a bicarbonate salt and a second buffering agent. 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.

Suitable carbonate salts and bicarbonate salts are described above. The amount of carbonate salt or bicarbonate salt used in the binary buffer system is an amount that is sufficient, when used with the second buffering agent, to raise salivary pH to a pH of about 7.8 or more, preferably about 8.5 or more, and more preferably about 9 or more (e.g., about 9-11), irrespective of the starting pH. In certain instances, the amount of the second buffering agent in the binary buffer system is greater than or equal to the amount of the carbonate salt or bicarbonate salt. For example, the weight ratio of the second buffering agent to the carbonate salt or bicarbonate salt can be 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 3:1. In certain other instances, the amount of the second buffering agent in the binary buffer system is less than or equal to the amount of the carbonate salt or bicarbonate salt. For example, the weight ratio of the second buffering agent to the carbonate salt or bicarbonate salt can be 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 1:3.

The second buffering agent is generally selected from a metal oxide such as magnesium oxide or aluminum oxide; a citrate salt such as sodium citrate, potassium citrate, calcium citrate, magnesium citrate, and ammonium citrate; a phosphate salt such as monobasic sodium phosphate, dibasic sodium phosphate, monobasic potassium phosphate, dibasic potassium phosphate, monobasic calcium phosphate, dibasic calcium phosphate, monobasic magnesium phosphate, dibasic magnesium phosphate, monobasic ammonium phosphate, and dibasic ammonium phosphate; a borate salt such as sodium borate, potassium borate, calcium borate, magnesium borate, and ammonium borate; an ascorbate salt such as potassium ascorbate or sodium ascorbate; an acetate salt such as potassium acetate or sodium acetate; and alkaline starch. However, one skilled in the art will appreciate that any metal oxide or salt of citric acid, phosphoric acid, boric acid, ascorbic acid, or acetic acid is suitable for use in the buffer systems of the present invention. The amount of the second buffering agent used in the binary buffer system is an amount that is sufficient, when used with the carbonate salt or bicarbonate salt, to raise salivary pH to a pH of about 7.8 or more, preferably about 8.5 or more, and more preferably about 9 or more (e.g., about 9-11), irrespective of the starting pH. In some embodiments, a metal oxide such as magnesium oxide or aluminum oxide is the preferred second buffering agent. In a particularly preferred embodiment, the metal oxide is amorphous magnesium oxide.

Alternatively, in yet another embodiment, the buffer systems of the present invention are binary buffer systems comprising a metal oxide and a citrate, phosphate, or borate salt. 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 5 about minutes, at least about 10 minutes, at least about 20 minutes, or at least about 60 minutes.

Suitable metal oxides include, without limitation, magnesium oxide and aluminum oxide. Suitable citrate, phosphate, and borate salts include, without limitation, essentially any salt of citric acid, phosphoric acid, or boric acid known in the art such as those described above. In certain instances, the binary buffer system comprises a metal oxide and a citrate salt. In certain other instances, the binary buffer system com-

prises a metal oxide and a phosphate salt. In further instances, the binary buffer system comprises a metal oxide and a borate salt. The amount of the metal oxide used in the binary buffer system is an amount that is sufficient, when used with the citrate, phosphate, or borate salt, to raise salivary pH to a pH of about 7.8 or more, preferably about 8.5 or more, and more preferably about 9 or more (e.g., about 9-11), irrespective of the starting pH. Similarly, the amount of the citrate, phosphate, or borate salt used in the binary buffer system is an amount that is sufficient, when used with the metal oxide, to raise salivary pH to a pH of about 7.8 or more, preferably about 8.5 or more, and more preferably about 9 or more (e.g., about 9-11), irrespective of the starting pH.

In certain instances, the amount of the metal oxide in the binary buffer system is greater than or equal to the amount of the citrate, phosphate, or borate salt. For example, the weight ratio of the metal oxide to the citrate, phosphate, or borate salt can be 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 3:1. In certain other instances, the amount of the metal oxide in the binary buffer system is less than or equal to the amount of the citrate, phosphate, or borate salt. For example, the weight ratio of the metal oxide to the citrate, phosphate, or borate salt can be 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 1:3.

Alternatively, in still yet another embodiment, the buffer systems of the present invention are ternary buffer systems comprising a carbonate salt, a bicarbonate salt, and a third buffering agent. 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 5 about minutes, at least about 10 minutes, at least about 20 minutes, or at least about 60 minutes. The procedure described above for determining an appropriate weight ratio for each buffer system component can also be applied to ternary buffer systems.

Suitable carbonate salts and bicarbonate salts are described above. The amount of carbonate salt and bicarbonate salt used in the ternary buffer system is an amount that is sufficient, when used with the third buffering agent, to raise salivary pH to a pH of about 7.8 or more, preferably about 8.5 or more, and more preferably about 9 or more (e.g., about 9-11), irrespective of the starting pH.

The third buffering agent is generally selected from a metal oxide, a citrate salt a phosphate salt, a borate salt, an ascorbate salt such as potassium ascorbate or sodium ascorbate, an acetate salt such as potassium acetate or sodium acetate, and alkaline starch. Suitable metal oxides include, without limitation, magnesium oxide and aluminum oxide. Suitable citrate, phosphate, and borate salts include, without limitation, any salt of citric acid, phosphoric acid, or boric acid known in the art such as those described above. The amount of the third buffering agent used in the ternary buffer system is an amount that is sufficient, when used with the remaining components, to raise salivary pH to a pH of about 7.8 or more, preferably about 8.5 or more, and more preferably about 9 or more (e.g., about 9-11), irrespective of the starting pH. In some embodiments, a metal oxide such as magnesium oxide or aluminum oxide is the preferred third buffering agent. In a particularly preferred embodiment, the metal oxide is amorphous magnesium oxide.

In certain instances, the amount of the carbonate salt or bicarbonate salt in the ternary buffer system is greater than or equal to the amount of the third buffering agent. For example, the weight ratio of the carbonate salt or bicarbonate salt to the third buffering agent can be 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 3:1. In certain other instances, the amount of the carbonate salt or bicarbonate salt in the ternary buffer system is less than or equal to the amount of the third buffering agent. For example, the weight ratio of the carbonate salt or bicarbonate salt to the third buffering agent can be 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 1:3.

The ternary buffer systems of the present invention, in some of the most preferred embodiments, contain sodium carbonate, sodium bicarbonate, and amorphous magnesium oxide. In certain instances, the amount of sodium bicarbonate is greater than or equal to the amount of sodium carbonate. For example, the weight ratio of sodium bicarbonate to sodium carbonate can be 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 3:1. In certain other instances, the amount of amorphous magnesium oxide is greater than or equal to the combined amount of sodium carbonate and sodium bicarbonate. For example, the weight ratio of amorphous magnesium oxide to sodium carbonate and sodium bicarbonate can be 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 3:1.

Alternatively, in a further embodiment, the buffer systems of the present invention are buffer systems comprising 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. 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 5 about minutes, at least about 10 minutes, at least about 20 minutes, or at least about 60 minutes.

Suitable carbonate salts and bicarbonate salts are described above. The amount of carbonate salt or bicarbonate salt used in the buffer system is an amount that is sufficient, when used with the remaining components, to raise salivary pH to a pH of about 7.8 or more, preferably about 8.5 or more, and more preferably about 9 or more (e.g., about 9-11), irrespective of the starting pH.

The two or more buffering agents are generally selected from a metal oxide, a citrate salt, a phosphate salt, a borate salt, an ascorbate salt, an acetate salt, and alkaline starch. Suitable metal oxides include, without limitation, magnesium oxide and aluminum oxide. Suitable citrate, phosphate, borate, ascorbate, and acetate salts include, without limitation, essentially any salt of citric acid, phosphoric acid, boric acid, ascorbic acid, or acetic acid known in the art such as those described above. The amount of the additional buffering agents used in the buffer system is an amount that is sufficient, when used with the carbonate salt or bicarbonate salt, to raise salivary pH to a pH of about 7.8 or more, preferably about 8.5 or more, and more preferably about 9 or more (e.g., about 9-11), irrespective of the starting pH.

In certain instances, the buffer system comprises a carbonate salt or a bicarbonate salt, a metal oxide, and a citrate, phosphate, or borate salt. In certain other instances, the buffer system comprises a carbonate salt or a bicarbonate salt, a citrate salt, and a phosphate salt. In certain instances, the buffer system comprises a carbonate salt or a bicarbonate salt, a citrate salt, and a borate salt. In certain other instances, the buffer system comprises a carbonate salt or a bicarbonate salt, a phosphate salt, and a borate salt. Preferably, the metal oxide is amorphous magnesium oxide.

In certain instances, the amount of the carbonate salt or bicarbonate salt in the buffer system is greater than or equal to the amount of the metal oxide or the citrate, phosphate, or

borate salt. For example, the weight ratio of the carbonate salt or bicarbonate salt to the metal oxide or the citrate, phosphate, or borate salt can be 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 3:1. In certain other instances, the amount of the carbonate salt or bicarbonate salt in the buffer system is less than or equal to the amount of the metal oxide or the citrate, phosphate, or borate salt. For example, the weight ratio of the carbonate salt or bicarbonate salt to the metal oxide or the citrate, phosphate, or borate salt can be 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 1:3.

While the foregoing discussion has focused on the ability of the buffer system to alter salivary pH to favor substantial conversion to the un-ionized form of a therapeutic agent, it is conceivable that the buffer system may also have subsidiary beneficial effects on the extent of absorption across the oral mucosa. For example, the buffer system may create a final salivary pH that in turn affects the molecular configuration of the therapeutic agent in a way in which absorption across the oral mucosa is increased. It is to be understood that these subsidiary beneficial effects of the buffer system are within the general scope of the buffer system and compositions herein described.

C. Dosage Forms

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), pills, capsules, lozenges, gums, powders, solutions, suspensions, emulsions, aerosols, or the like. Preferably, the dosage form is a chewing gum, dissolving tablet, chewable tablet, candy, or lozenge.

While each subject or patient possesses unique factors that may affect the rate and extent of absorption of the therapeutic agents described herein, dosage forms such as chewing gums, chewable tablets, dissolving tablets, or lozenges containing a buffer system described herein offer advantages over the traditional dosage forms for oral administration (i.e., Ambien®). For example, each of these dosage forms avoids hepatic first pass metabolism, degradation within the gastrointestinal tract, and drug loss during absorption. Consequently, the amount of therapeutic agent required per dose is less than that which would be required if formulated, for example, in a pill or tablet for oral administration. Similarly, the bioavailability of the therapeutic agent is increased, thereby reducing the time to onset of therapeutic activity as compared to traditional dosage forms for oral administration (see, Example 5 below).

In addition, the preferred dosage forms of the present invention (e.g., chewing gums, chewable tablets, dissolving tablets, lozenges) containing a buffer system described herein offer advantages over dosage forms for oral mucosal administration that do not contain the buffer system (i.e., zolpidem FlashDose® tablet). Importantly, because the buffer system in the dosage forms of the present invention helps convert substantially all of the therapeutic agent from its ionized form to its un-ionized form, the bioavailability of the therapeutic agent is increased, thereby reducing the time to onset of therapeutic activity as compared to dosage forms for oral mucosal administration that do not contain the buffer system. For example, U.S. Patent Publication No. 2003/0165566 discloses that the buccally administered zolpidem FlashDose® tablet has a pharmacokinetic profile similar to that observed for the orally administered Ambien® tablet. As such, the zolpidem compositions of the present invention surpass both commercial tablet compositions by providing an increase in the bioavailability of zolpidem and a reduction in the time to onset of therapeutic activity.

As used herein, the term "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 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 this invention.

As used herein, the term "carrier" refers 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, polyacrylic acid (e.g., Carbopol), calcium silicate, calcium phosphate, dicalcium phosphate, calcium sulfate, kaolin, sodium chloride, polyethylene 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 (i.e., dissolving 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, 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%.

1. Chewing Gums

When the dosage form is a chewing gum, the compositions of the present invention comprise a hypnotic agent or a pharmaceutically acceptable salt thereof, a carrier such as a gum base, a binary or ternary 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 from about 0.001% to about 10.0% by weight of the hypnotic agent (in whatever chosen form, measured as per its free base form), more typically from about 0.01% to about 5.0%, and still more typically from about 0.1% to about 3.0%. One skilled in the art understands that the foregoing percentages will vary depending upon the particular source of hypnotic agent utilized, the amount of hypnotic agent desired in the final formulation, as well as on the particular release rate of hypnotic agent desired. The binary or ternary buffer system of the chewing gum composition provides for 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% 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 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, 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% 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 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 binary or ternary buffer system as described herein. Methods for preparing a centerfill chewing gum are described, for example, in U.S. Pat. No. 3,806,290, which is hereby incorporated by reference in its entirety.

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.

2. Tablets

When the dosage form is a tablet such as a dissolving tablet (i.e., disintegrating tablet) or chewable tablet, the compositions of the present invention comprise a hypnotic agent or a pharmaceutically acceptable salt thereof, a carrier such as a binder, and a binary or ternary buffer system. The tablet composition may further comprise 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 from about 0.001% to about 10.0% by weight of the hypnotic agent (in whatever chosen form, measured as per its free base form), and more typically from about 1.0% to about 5.0%. In some embodiments, about 4.0% by weight of the hypnotic agent is used. One skilled in the art understands that the foregoing percentages will vary depending upon the particular source of hypnotic agent utilized, the amount of hypnotic agent desired in the final formulation, as well as on the particular release rate of hypnotic agent desired. The binary or ternary buffer system of the tablet composition provides for 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 15 minutes following administration. How-

ever, 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) 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 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 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 about 1 to about 10. Without being bound to any particular theory, the protecting agent reduces the adhesion between the therapeutic agent and the binder so that the therapeutic agent may be more easily released from the binder. In this way, the therapeutic agent may be delivered across the mucous membranes of the oral cavity within about 5 to about 20 minutes, preferably within about 10 minutes. Materials suitable as protecting agents are discussed in detail above and may be used alone or in combination in the tablet compositions of the present invention.

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. 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 binder 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 binary or ternary buffer system as described herein.

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, e.g., two or more hypnotic agents or one or more hypnotic agents in combination with one or more non-hypnotic therapeutic agents. For example, with a bi-layered tablet, the first layer contains a hypnotic agent and the second layer contains the same or different hypnotic agent or a non-hypnotic therapeutic 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 the hypnotic agent, 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 the hypnotic agent 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 binary or ternary buffer system as described herein.

In still other instances, the combination of hypnotic agents with or without non-hypnotic therapeutic 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.

3. Lozenges

When the dosage form is a lozenge or candy, the compositions of the present invention comprise a hypnotic agent or a pharmaceutically acceptable salt thereof, a carrier such as a binder, and a binary or ternary buffer system. The lozenge or candy composition may further comprise 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 from about 0.001% to about 10.0% by weight of the hypnotic agent (in whatever chosen form, measured as per its free base form), and more typically from about 1.0% to about

5.0%. In some embodiments, about 4.5% by weight of the hypnotic agent is used. One skilled in the art understands that the foregoing percentages will vary depending upon the particular source of hypnotic agent utilized, the amount of hypnotic agent desired in the final formulation, as well as on the particular release rate of hypnotic agent desired. The binary or ternary buffer system of the lozenge composition provides for 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 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) 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 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 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 about 1 to about 10. Without being bound to any particular theory, the protecting agent reduces the adhesion between the therapeutic agent and the binder so that the therapeutic agent may be more easily released from the binder. In this way, the therapeutic agent may be delivered across the mucous membranes of the oral cavity within about 5 to about 20 minutes, preferably within about 10 minutes. Materials suitable as protecting agents are discussed in detail above and may be used alone or in combination in the lozenge compositions of the present invention.

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 tablet 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 certain instances, the lozenge 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 binder 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 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 binary or ternary buffer system as described herein.

In certain other instances, the lozenge composition of the present invention is multilayered. In this way, the lozenge can be designed to provide more than one therapeutic agent, e.g. two or more hypnotic agents or one or more hypnotic agents in combination with one or more non-hypnotic therapeutic agents. For example, with a bi-layered lozenge, the first layer contains a hypnotic agent and the second layer contains the same or different hypnotic agent or a non-hypnotic therapeutic agent. Typically, the first layer comprises the dissolving portion of the lozenge, 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 the hypnotic agent, 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 the hypnotic agent in the dissolving portion of the lozenge. 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 binary or ternary buffer system as described herein.

In still other instances, the combination of hypnotic agents with or without non-hypnotic therapeutic agents need not take the form of a multilayered lozenge, but instead comprises a single homogenous lozenge 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 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.

D. Methods of Administration

The compositions of the present invention are useful in therapeutic applications, e.g., for treating a sleep disorder. Importantly, the compositions of the present invention provide the rapid and predictable delivery of a hypnotic agent across the oral mucosa with surprisingly low inter-subject variability in terms of maximum plasma concentration (C_{max}) and the time to reach the maximum plasma concentration (T_{max}) by raising the pH of saliva to a pH greater than about 7.8, irrespective of the starting pH of saliva. In particular, the delivery of the therapeutic agent across the oral mucosa avoids hepatic first pass metabolism, degradation within the gastrointestinal tract, and drug loss during absorption. As a result, the therapeutic agent reaches the systemic circulation in a substantially shorter period of time and at a substantially higher concentration than with traditional oral (e.g., tablet) administration.

In addition, the compositions of the present invention offer advantages over compositions for oral mucosal administration that do not contain the buffer system described herein. In particular, because the buffer system in the compositions of the present invention helps convert substantially all of the therapeutic agent from its ionized form to its un-ionized form, the therapeutic agent reaches the systemic circulation in a substantially shorter period of time (e.g., reducing the time to onset of therapeutic activity) and at a substantially higher concentration than with compositions for oral mucosal administration that do not contain the buffer system.

The compositions of the present invention have particular utility in the area of human and veterinary therapeutics. Generally, administered dosages will be effective to deliver picomolar to micromolar concentrations of the hypnotic agent to the appropriate site.

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.

The oral mucosa is composed of an outermost layer of stratified squamous epithelium. Beneath this layer lies a basement membrane, i.e., the lamina propria, followed by the submucosa as the innermost layer. The epithelium of the oral mucosa is similar to the stratified squamous epithelia found in the rest of the body in that it contains a mitotically active basal cell layer, advancing through a number of differentiating intermediate layers to the superficial layers, where cells are shed from the surface of the epithelium (Gandhi et al., *Ind. J. Pharm. Sci.,* 50:145-152 (1988)). For example, the epithelium of the buccal mucosa is about 40-50 cell layers thick, while that of the sublingual epithelium contains somewhat fewer cell layers. The epithelial cells increase in size and become flatter as they travel from the basal layers to the superficial layers.

The turnover time for buccal mucosal epithelium, estimated at 5-6 days, is representative of the turnover time for sublingual mucosal epithelium as well as other epithelia in the oral mucosa (Harris et al., *J. Pharm. Sci.,* 81:1-10 (1992)). The thickness of the oral mucosa varies depending on the site in the oral cavity. For example, the buccal mucosa measures at about 500-800 μm in thickness, while the hard and soft palatal mucosa, the sublingual mucosa, the ventral tongue, and the gingival mucosa measure at about 100-200 μm in thickness. The composition of the epithelium also varies depending on the site in the oral cavity. For example, the mucosae of areas subject to mechanical stress (i.e., the gingivae and hard palate) are keratinized similar to the epidermis. However, the mucosae of the soft palate, the sublingual region, and the buccal region are not keratinized (Harris et al., supra). The keratinized epithelia contain neutral lipids like ceramides and acylceramides, which have been associated with providing a barrier function. As a result, these epithelia are relatively impermeable to water. In contrast, non-keratinized epithelia, such as sublingual and buccal epithelia, do not contain acylceramides and have only small amounts of ceramide (Wertz et al., *Crit. Rev. Ther. Drug Carr. Sys.,* 8:237-269 (1991); Squier et al., *J. Invest. Dermat.,* 96:123-126 (1991); Squier et al., in *Oral Mucosal Drug Delivery*, Ed. M. J. Rathbone, Marcel Dekker, Inc., New York, N.Y., 1-26 (1996)). Non-keratinized epithelia also contain small amounts of neutral but polar lipids, e.g., cholesterol sulfate and glucosyl ceramides. As such, these epithelia have been found to be considerably more permeable to water than keratinized epithelia (Harris et al., supra; Wertz et al., supra; Squier et al., supra, 1991).

In general, the oral mucosa is a somewhat leaky epithelia intermediate between that of the epidermis and intestinal mucosa. For example, the permeability of the buccal mucosa is estimated to be about 4-4000 times greater than that of skin (Galey et al., *J. Invest. Dermat.,* 67:713-717 (1976)). The permeability of different regions of the oral mucosa generally decrease in the order of sublingual mucosa greater than buccal mucosa, and buccal mucosa greater than palatal mucosa (Harris et al., supra). This permeability is generally based upon 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.

The epithelial cells of the oral mucosa are surrounded by mucus comprising primarily complexes of proteins and carbohydrates that may or may not be attached to certain regions on the cell surface. The mucus may play a role in cell-cell

adhesion, as well as acting as a lubricant, allowing cells to move relative to one another (Tabak et al., *J. Oral Pathol.,* 11:1-17 (1982)). In stratified squamous epithelia found elsewhere in the body, mucus is synthesized by specialized mucus secreting cells such as goblet cells; however, in the oral mucosa, mucus is secreted by the major and minor salivary glands as part of saliva (Tabak et al., supra; Rathbone et al., *Adv. Drug Del. Rev.,* 13:1-22 (1994)). At physiological pH, the mucus network carries a negative charge due to the sialic acid and sulfate residues present on the carbohydrates. At this pH, mucus can form a strongly cohesive gel structure that binds to the epithelial cell surface as a gelatinous layer (Gandhi et al., supra). Without being bound to any particular theory, the buffer systems of the present invention neutralize the sialic acid residues present on the carbohydrates and prevent them from interacting with the therapeutic agent, thereby further enhancing drug permeation.

Another feature of the environment of the oral activity is the presence of saliva produced by the salivary glands. Saliva is the protective fluid for all tissues of the oral cavity. Saliva is an aqueous fluid with about 1% organic and inorganic materials. The major determinant of the salivary composition is the flow rate, which in turn depends upon factors such as the time of day, the type of stimulus, and the degree of stimulation. The salivary pH typically ranges from about 5.5 to about 7.0, depending on the flow rate. For example, at high flow rates, the sodium and bicarbonate concentrations increase, leading to an increase in the pH. Because the daily salivary volume is between about 0.5 to about 2 liters, the oral cavity provides an aqueous environment for the hydration and/or dissolution of the oral mucosal dosage forms of the present invention.

The sublingual mucosa is the most highly permeable region of the oral cavity, and provides rapid absorption and high bioavailability of a drug in a convenient, accessible, and well-accepted route of administration (Harris et al., supra). Suitable sublingual dosage forms include, without limitation, tablets (e.g., quick-dissolving, slow-dissolving), lozenges, candy, and soft gelatin capsules filled with liquid drug. Such systems create a very high drug concentration in the sublingual region before they are systemically absorbed across the sublingual mucosa. As a result, the sublingual mucosa is particularly well-suited for producing a rapid onset of action, and sublingual dosage forms can be used to deliver drugs with shorter delivery period requirements and/or less frequent dosing regimens. Although the buccal mucosa is considerably less permeable than the sublingual area, rapid absorption and high bioavailability of a drug can also be observed with buccal administration. Suitable buccal dosage forms include, without limitation, chewing gums, tablets (e.g., quick-dissolving, slow-dissolving), lozenges, candy, and the like. Both the buccal mucosa and the sublingual mucosa are far superior to the gastrointestinal tract for providing increased absorption and bioavailability of a drug.

To increase the permeability of drugs through the oral mucosa, penetration enhancers can be included in the dosage forms of the present invention. The penetration enhancers may be of the type that alters the nature of the oral mucosa to enhance penetration, or of the type that alters the nature of the therapeutic agent to enhance penetration through the oral mucosa. Suitable penetration enhancers include, without limitation, polyoxyethylene 23-lauryl ether, aprotin, azone, benzalkonium chloride, cetylpyridinium chloride, cetyltrimethylammonium bromide, cyclodextrin, dextran sulfate, lauric acid, propylene glycol, lysophosphatidylcholine, menthol, methoxysalicylate, methyloleate, oleic acid, phosphatidylcholine, polyoxyethylene, polysorbate 80, sodium ethylenediaminetetraacetic acid ("EDTA"), sodium deoxycholate, sodium glycocholate, sodium glycodeoxycholate, sodium lauryl suflate, sodium salicylate, sodium taurocholate, sodium taurodeoxycholate, as well as certain sulfoxides and glycosides, and combinations thereof.

IV. EXAMPLES

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

Example 1

Zolpidem Membrane Assay

This example illustrates the beneficial effects of pH adjustment on membrane penetration for a zolpidem dosage form.

The effect of pH adjustment on the extent of ionization, and hence, the extent to which a therapeutic agent will traverse the mucous membrane can be demonstrated using a membrane assay; see, e.g., Kansy et al., *J. Med. Chem.,* 41:1007-1010 (1998); and Avdeef, *Curr. Topics Med. Chem.,* 1:277-351 (2001). This assay uses a lipid-coated membrane to predict lipid mucosal membrane penetration. The membrane apparatus consists of a dodecane membrane sandwiched between a donor and acceptor cell. The lipid-coated membrane is less porous then the mucous membrane of the oral cavity. Thus, the enhancement seen in the membrane assay is very likely to be magnified in vivo.

Membrane assays were performed using zolpidem tartrate solutions at a pH of 5.8, 6.8, and 7.8. The alkaline pH values of 7.8 were adjusted using freshly prepared 0.01 M sodium bicarbonate/sodium carbonate buffer solution. The acidic pH of 5.8 was achieved using a 0.01 M acetate buffer solution (a mixture of sodium acetate and acetic acid). The neutral pH of 6.8 was achieved by adding 0.01 M acetate solution to the sodium bicarbonate/sodium carbonate buffer solution. Permeation through the membrane was measured by determining the concentration of zolpidem in the acceptor cell and is expressed as P_e (effective permeability in centimeters per second). As shown in Table 1 below, the effective permeability of zolpidem increased by more than 53% at a pH of 7.8 relative to a pH of 6.8 and 129% relative to a pH of 5.8. FIG. **1** shows a bar chart illustrating the relationship between pH and zolpidem membrane permeability.

TABLE 1

Effective permeability (P_e) of zolpidem in a membrane assay.

pH	P_e (cm/s)
5.8	19.8
6.8	29.6
7.8	45.3

Example 2

Zolpidem Gum Compositions

This example illustrates the zolpidem chewing gum compositions of the present invention.

Zolpidem can be formulated as a chewing gum composition as described above. In these embodiments, the unit dose or serving of the chewing gum comprises from about 0.1 to about 100 milligrams (mg) zolpidem (as measured in its tartrate salt form), preferably from about 1 to about 50 mg, and more preferably from about 2 to about 25 mg. In other

embodiments, the unit dose comprises from about 2 to about 20 mg zolpidem, preferably from about 5 to about 15 mg. Extra zolpidem, for example, up to from about 10% to about 25% by weight, can be added as "overage" or as the amount that may be expected to be "washed away" and not otherwise released or absorbed during mastication.

In another embodiment, the unit dose or serving of the chewing gum comprises from about 0.81 to about 42 mg zolpidem in its base form, and more preferably from about 1.64 to about 20.5 mg. In other embodiments, the unit dose comprises from about 1.64 to about 16.4 mg zolpidem in its free base form, preferably from about 1.64 to about 12.3 mg, and more preferably from about 1.64 to about 8.2 mg, e.g., about 1.64, 2.46, 3.28, 4.1, 4.92, 5.78, 6.56, 7.38, or 8.2 mg. In additional embodiments, the unit dose comprises a mixture of zolpidem in free base form and salt form (e.g., zolpidem tartrate).

Given in weight percentages, the zolpidem chewing gum composition comprises from about 0.001% to about 10.0% zolpidem (in whatever chosen form, measured as per its free base form), preferably from about 0.05% to about 2.0%, and more preferably from about 0.1% to about 1.0%. In some embodiments, about 0.25% zolpidem is used. One skilled in the art understands that the foregoing percentages 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. The buffer system of the zolpidem chewing gum composition provides for 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).

A zolpidem chewing gum was made according to the following procedure. Silicon dioxide USP (0.35 kg) was passed through a #20 mesh screen, and then loaded into a blender containing 0.810 kg mannitol granular USP and 9.569 kg Pharmagum™ C. The material was blended for 10 minutes. Zolpidem tartrate EP (0.034 kg) was ground with the silicon dioxide (0.02 kg) using a mortar and pestle. The remaining silicon dioxide, along with 0.228 kg magnesium stearate, was added into the mortar while continuing to grind. The ground materials were transferred into a plastic bag, and the mortar was rinsed using 0.01 kg silicone dioxide, and transferred into the bag. The contents of the bag were then blended for five minutes.

Equal parts of the blended bag contents and the blended mannitol gum base mixture were blended for an additional five minutes. This process was repeated until all the zolpidem and gum base mixture had been blended together. Sodium carbonate (0.110 kg), sodium bicarbonate (0.570 kg), gum acacia (0.43 kg), xanthan gum (0.013 kg), and aspartame (0.072 kg) were then loaded into the blender along with natural and artificial flavors and blended for ten minutes with 0.090 kg of silicon dioxide. The flavors used were as follows: natural and artificial grape flavor S.D. (0.215 kg), natural and artificial cherry flavor (0.108 kg), natural and artificial fruit punch flavor S.D. (0.180 kg), natural cherry WONF DURAROME® flavor (0.215 kg), and natural passion fruit type DURAROME® flavor (0.035 kg).

The blend was passed through a #12 mesh screen and then blended for an additional 15 minutes. Magnesium stearate (0.114 kg) was passed through a #20 mesh screen and added to the blend and blended for five minutes. The blend was collected and placed in plastic bags. Two silica gel desiccant bags were placed around the plastic bags to absorb ambient moisture. The blend was then compressed into tablets. By using the above-described procedure, the average particle size of the drug (i.e., zolpidem) in the chewing gum is about 20 microns, as compared to a typical average drug particle size of from about 75 to about 100 microns. In addition, the average particle size of the drug in the chewing gum is less than or equal to the average particle size of the carrier ingredients (e.g., gum base, binders, etc.).

The zolpidem chewing gum composition of the present invention can be used, e.g., for treatment of insomnia; see, Holm et al., *Drugs,* 59:865-889 (2000). In certain instances, after the introduction of a serving size piece of the chewing gum composition into the mouth, the subject chews the chewing gum as is normally done with any non-medicated type of chewing gum for about 5 to about 20 minutes, at approximately an average rate of about 10 to about 45 chews per minute. The gum is then discarded.

A typical dosage form of the zolpidem chewing gum of the present invention is designed to produce an average plasma concentration of at least from about 20 to about 300 nanograms of zolpidem per milliliter of plasma. For example, a 5 mg zolpidem chewing gum can be designed to produce a mean peak plasma concentration within the range of from about 20 to about 100 nanograms of zolpidem per milliliter of plasma within about 5 minutes to about 2 hours. Similarly, a 10 mg zolpidem chewing gum can be designed to produce a mean peak plasma concentration within the range of from about 100 to about 300 nanograms of zolpidem per milliliter of plasma within about 5 minutes to about 2 hours.

The chewing gum compositions of the present invention provide a convenient, reliable, practical, and painless system for delivering zolpidem across the oral mucosa. Notably, the chewing gum compositions are capable of rapidly delivering zolpidem with low inter-subject variability in terms of maximum plasma concentration (C_{max}) and the time to reach the maximum plasma concentration (T_{max}) so that a therapeutically effective amount of zolpidem enters the bloodstream within about 30 minutes, 20 minutes, 15 minutes, 10 minutes, 5 minutes, or even within about 1-2 minutes after zolpidem is released from the carrier.

Example 3

Zolpidem Tablet Compositions

This example illustrates the slow-dissolving, quick-dissolving, and chewable zolpidem tablet compositions of the present invention.

Zolpidem can be formulated as a tablet composition as described above. In these embodiments, the unit dose or serving of the tablet comprises from about 0.1 to about 100 milligrams (mg) zolpidem (as measured in its tartrate salt form), preferably from about 1 to about 50 mg, and more preferably from about 2 to about 25 mg. In other embodiments, the unit dose comprises from about 2 to about 20 mg zolpidem, preferably from about 2 to about 15 mg, and more preferably from about 2 to about 10 mg, e.g., about 2, 3, 4, 5, 6, 7, 8, 9, or 10 mg. In particularly preferred embodiments, the unit dose comprises a dose of zolpidem that is less than the dose typically used in commercial oral tablets, but possesses comparable or greater bioavailability and onset of therapeutic activity as well as lower variability of drug absorption. In such embodiments, unit doses of from about 2 to about 5 mg zolpidem are preferred, with unit doses of about 4 mg zolpidem being particularly preferred. Extra zolpidem, for example, up to from about 10% to about 25% by weight, can be added as "overage" or as the amount that may be expected to be "washed away" and not otherwise released or absorbed during tablet dissolution and/or mastication.

In another embodiment, the unit dose or serving of the tablet comprises from about 0.81 to about 42 mg zolpidem in its base form, and more preferably from about 1.64 to about 20.5 mg. In other embodiments, the unit dose comprises from about 1.64 to about 16.4 mg zolpidem in its free base form, preferably from about 1.64 to about 12.3 mg, and more preferably from about 1.64 to about 8.2 mg, e.g., about 1.64, 2.46, 3.28, 4.1, 4.92, 5.78, 6.56, 7.38, or 8.2 mg. In additional embodiments, the unit dose comprises a mixture of zolpidem in free base form and salt form (e.g., zolpidem tartrate).

Given in weight percentages, the zolpidem tablet composition comprises from about 0.001% to about 10.0% zolpidem (in whatever chosen form, measured as per its free base form), preferably from about 0.1% to about 8.0%, more preferably from about 1.0% to about 7.0%, and still more preferably from about 1.0% to about 5.0%. In some embodiments, about 4.0% zolpidem is used. One skilled in the art understands that the foregoing percentages 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. The buffer system of the zolpidem tablet composition provides for 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).

Zolpidem Slow-dissolving Tablets:

A zolpidem slow-dissolving tablet was made according to the following procedure. Magnesium stearate USP (0.5 kg) was passed through a #20 mesh screen, and then loaded into a blender containing 0.810 kg mannitol granular USP and 9.569 kg sorbitol. The material was blended for 10 minutes. Zolpidem tartrate EP (0.034 kg) was ground with the magnesium stearate (0.02 kg) using a mortar and pestle. The remaining silicon dioxide, along with 0.228 kg magnesium stearate was added into the mortar while continuing to grind. The ground materials were transferred into a plastic bag, and the mortar was rinsed using 0.01 kg silicone dioxide, and transferred into the bag. The contents of the bag were then blended for five minutes.

Equal parts of the blended bag contents and the blended mannitol mixture were blended for an additional five minutes. This process was repeated until all the zolpidem and mannitol mixture had been blended together. Sodium carbonate (0.110 kg), sodium bicarbonate (0.570 kg), gum acacia (0.43 kg), xanthan gum (0.013 kg), and aspartame (0.072 kg) were then loaded into the blender with natural and artificial flavors and blended for ten minutes with 0.090 kg of silicon dioxide. The flavors used were as follows: natural and artificial grape flavor S.D. (0.215 kg), natural and artificial cherry flavor (0.108 kg), natural and artificial fruit punch flavor S.D. (0.180 kg), natural cherry WONF DURAROME® flavor (0.215 kg), and natural passion fruit type DURAROME® flavor (0.035 kg).

The blend was passed through a #12 mesh screen and then blended for an additional 15 minutes. Magnesium stearate (0.114 kg) was passed through a #20 mesh screen and added to the blend and blended for five minutes. The blend was collected and placed in plastic bags. Two silica gel desiccant bags were placed around the plastic bags to absorb ambient moisture. The blend was then compressed into tablets. By using this procedure, the average particle size of the drug (i.e., zolpidem) in the slow-dissolving tablet is about 20 microns, as compared to a typical average drug particle size of from about 75 to about 100 microns. In addition, the average particle size of the drug in the slow-dissolving tablet is less than or equal to the average particle size of the carrier ingredients (e.g., gum base, binders, etc.).

A second zolpidem slow-dissolving tablet was made according to the formulation shown in Table 2 and the following procedure. Three separate blends of silicon dioxide with zolpidem, sodium bicarbonate, and sodium carbonate; mannitol and sorbitol; and spearmint flavor, sucralose, stearic acid, and magnesium stearate were prepared. The three blends were screened separately and mixed to form a single blend. The single blend was then compressed into tablets after testing for content uniformity. By using this procedure, the average particle size of the drug (i.e., zolpidem) in the slow-dissolving tablet is about 20 microns, which is less than or equal to the average particle size of the carrier ingredients (e.g., gum base, binders, etc.). The unit weight for each tablet was 250 mg. The pH of the tablet was about 9.8 and remained stable. These tablets dissolve within about 10 minutes following sublingual administration.

TABLE 2

Zolpidem slow-dissolving tablet formulation.

Material	Unit Quantity (mg)	Batch Quantity (g)
Sodium Carbonate, NF	17.000	357.000
Sodium Bicarbonate USP	23.000	483.000
Zolpidem Tartrate, EP	10.000	210.000
Mannitol, USP	40.000	840.000
Sorbitol, NF	136.000	2856.000
Natural & Artificial Spearmint Flavor	6.500	136.500
Sucralose, NF	1.000	21.000
Silicon Dioxide, USP	5.500	115.500
Stearic Acid, NF	3.500	73.500
Magnesium Stearate, NF	7.500	157.500

The batch quantity formulation produces 21,000 unit doses.

Zolpidem Quick-dissolving Tablets:

A zolpidem quick-dissolving tablet was made according to the following procedure. Mannitol (3.633 kg) and sorbitol (0.469 kg) were blended for ten minutes. Sodium carbonate (0.330 kg), sodium bicarbonate (0.165 kg), natural peppermint flavor (0.125 kg), natural menthol flavor (0.025 kg), and sucralose (0.020 kg) were blended separately for ten minutes. Magnesium stearate (0.075 kg), and zolpidem tartrate (0.034 kg) were blended for ten minutes and then passed through a #12 mesh screen. The blended mixtures were then added together and compressed into tablets. By using this procedure, the average particle size of the drug (i.e., zolpidem) in the quick-dissolving tablet is about 20 microns, as compared to a typical average drug particle size of from about 75 to about 100 microns. In addition, the average particle size of the drug in the quick-dissolving tablet is less than or equal to the average particle size of the carrier ingredients (e.g., gum base, binders, etc.).

A second zolpidem quick-dissolving tablet was made according to the formulation shown in Table 3 and the following procedure. Three separate blends of silicon dioxide with zolpidem, sodium carbonate, and sodium bicarbonate; mannitol and sorbitol; and polyethylene glycol, spearmint flavor, sucralose, magnesium stearate, crospovidone, and croscarmellose sodium were prepared. The three blends were screened separately and mixed to form a single blend. The single blend was then compressed into tablets after testing for content uniformity. By using this procedure, the average particle size of the drug (i.e., zolpidem) in the quick-dissolving tablet is about 20 microns, which is less than or equal to the average particle size of the carrier ingredients (e.g., gum base, binders, etc.). The unit weight for each tablet was 250 mg. The

pH of the tablet was about 9.8 and remained stable. These tablets dissolve within about 5 minutes following sublingual administration.

TABLE 3

Zolpidem quick-dissolving tablet formulation.

Material	Unit Quantity (mg)	Batch Quantity (g)
Sodium Carbonate, NF	17.000	357.000
Sodium Bicarbonate USP	23.000	483.000
Zolpidem Tartrate, EP	10.000	210.000
Mannitol, USP	40.000	840.000
Sorbitol, NF	103.500	2173.500
Crospovidone, NF	12.500	262.500
Croscarmellose Sodium, NF	12.500	262.500
Polyethylene Glycol 3350, NF	12.500	262.500
Natural & Artificial Spearmint Flavor	6.500	136.500
Sucralose, NF	1.000	21.000
Silicon Dioxide, USP	8.500	178.500
Magnesium Stearate, NF	3.000	63.000

The batch quantity formulation produces 21,000 unit doses.

Zolpidem Chewable Tablets:

A zolpidem chewable tablet was made according to the following procedure. Magnesium stearate USP (0.35 kg) was passed through a #20 mesh screen, and then loaded into a blender containing 0.810 kg mannitol granular USP, 9.569 kg sorbitol, and 0.020 kg stearic acid. The material was blended for 10 minutes. Zolpidem tartrate EP (0.034 kg) was ground with the magnesium stearate (0.02 kg) using a mortar and pestle. The remaining silicon dioxide, along with 0.228 kg magnesium stearate was added into the mortar while continuing to grind. The ground materials were transferred into a plastic bag, and the mortar was rinsed using 0.01 kg silicone dioxide, and transferred into the bag. The contents of the bag were then blended for five minutes.

Equal parts of the blended bag contents and the blended mannitol mixture were blended for an additional five minutes. This process was repeated until all the zolpidem and mannitol mixture had been blended together. Sodium carbonate (0.110 kg), sodium bicarbonate (0.570 kg), gum acacia (0.43 kg), xanthan gum (0.013 kg), and aspartame (0.072 kg) were then loaded into the blender with natural and artificial flavors and blended for ten minutes with 0.090 kg of silicon dioxide. The flavors used were as follows: natural and artificial grape flavor S.D. (0.215 kg), natural and artificial cherry flavor (0.108 kg), natural and artificial fruit punch flavor S.D. (0.180 kg), natural cherry WONF DURAROME® flavor (0.215 kg), and natural passion fruit type DURAROME® flavor (0.035 kg).

The blend was passed through a #12 mesh screen and then blended for an additional 15 minutes. Magnesium stearate (0.114 kg) was passed through a #20 mesh screen and added to the blend and blended for five minutes. The blend was collected and placed in plastic bags. Two silica gel desiccant bags were placed around the plastic bags to absorb ambient moisture. The blend was then compressed into tablets. By using this procedure, the average particle size of the drug (i.e., zolpidem) in the chewable tablet is about 20 microns, as compared to a typical average drug particle size of from about 75 to about 100 microns. In addition, the average particle size of the drug in the chewable tablet is less than or equal to the average particle size of the carrier ingredients (e.g., gum base, binders, etc.).

The zolpidem tablet composition of the present invention can be used, e.g., for treatment of insomnia. In certain instances, after the introduction of a chewable tablet into the mouth, the subject chews the chewable tablet as is normally done with any non-medicated type of chewable tablet at approximately an average rate of about 10 to about 45 chews per minute. In certain other instances, after the introduction of a dissolving tablet into the mouth, the subject holds the tablet underneath the tongue and either swallows while the tablet is dissolving or swallows after the tablet has dissolved.

A typical dosage form of the zolpidem tablet of the present invention is designed to produce an average plasma concentration of at least from about 20 to about 300 nanograms of zolpidem per milliliter of plasma. For example, a 5 mg zolpidem tablet can be designed to produce a mean peak plasma concentration within the range of from about 20 to about 100 nanograms of zolpidem per milliliter of plasma within about 5 minutes to about 2 hours. Similarly, a 10 mg zolpidem tablet can be designed to produce a mean peak plasma concentration within the range of from about 100 to about 300 nanograms of zolpidem per milliliter of plasma within about 5 minutes to about 2 hours.

The tablet compositions of the present invention provide a convenient, reliable, practical, and painless system for delivering zolpidem across the oral mucosa. Notably, the tablet compositions are capable of rapidly delivering zolpidem with low inter-subject variability in terms of maximum plasma concentration (C_{max}) and the time to reach the maximum plasma concentration (T_{max}) so that a therapeutically effective amount of zolpidem enters the bloodstream within about 30 minutes, 20 minutes, 15 minutes, 10 minutes, 5 minutes, or even within about 1-2 minutes after zolpidem is released from the carrier.

Example 4

Zolpidem Lozenge Compositions

This example illustrates the zolpidem lozenge compositions of the present invention.

Zolpidem can be formulated as a lozenge or candy composition as described above. In these embodiments, the unit dose or serving of the lozenge comprises from about 0.1 to about 100 milligrams (mg) zolpidem (as measured in its tartrate salt form), preferably from about 1 to about 50 mg, and more preferably from about 2 to about 25 mg. In other embodiments, the unit dose comprises from about 2 to about 20 mg zolpidem, preferably from about 2 to about 15 mg, and more preferably from about 2 to about 10 mg, e.g., about 2, 3, 4, 5, 6, 7, 8, 9, or 10 mg. In particularly preferred embodiments, the unit dose comprises a dose of zolpidem that is less than the dose typically used in commercial oral tablets, but possesses comparable or greater bioavailability and onset of therapeutic activity as well as lower inter-subject variability of drug absorption. In such embodiments, unit doses of from about 2 to about 5 mg zolpidem are preferred, with unit doses of about 4 mg zolpidem being particularly preferred. Extra zolpidem, for example, up to from about 10% to about 25% by weight, can be added as "overage" or as the amount that may be expected to be "washed away" and not otherwise released or absorbed during lozenge dissolution and/or mastication.

In another embodiment, the unit dose or serving of the lozenge comprises from about 0.81 to about 42 mg zolpidem in its base form, and more preferably from about 1.64 to about 20.5 mg. In other embodiments, the unit dose comprises from about 1.64 to about 16.4 mg zolpidem in its free base form, preferably from about 1.64 to about 12.3 mg, and more preferably from about 1.64 to about 8.2 mg, e.g., about 1.64, 2.46, 3.28, 4.1, 4.92, 5.78, 6.56, 7.38, or 8.2 mg. In additional

embodiments, the unit dose comprises a mixture of zolpidem in free base form and salt form (e.g., zolpidem tartrate).

Given in weight percentages, the zolpidem lozenge composition comprises from about 0.001% to about 10.0% zolpidem (in whatever chosen form, measured as per its free base form), preferably from about 0.1% to about 8.0%, more preferably from about 1.0% to about 7.0%, and still more preferably from about 1.0% to about 5.5%. In some embodiments, about 4.5% zolpidem is used. One skilled in the art understands that the foregoing percentages 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. The buffer system of the zolpidem lozenge composition provides for 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).

A zolpidem lozenge was made according to the formulation shown in Table 4 and the following procedure. Three separate blends of silicon dioxide with zolpidem, sodium carbonate, and sodium bicarbonate; Pharmaburst; and spearmint flavor, sucralose, magnesium stearate, and croscarmellose sodium were prepared. The three blends were screened separately and mixed to form a single blend. The single blend was then compressed into lozenges after testing for content uniformity. By using this procedure, the average particle size of the drug (i.e., zolpidem) in the lozenge is about 20 microns, as compared to a typical average drug particle size of from about 75 to about 100 microns. In addition, the average particle size of the drug in the lozenge is less than or equal to the average particle size of the carrier ingredients (e.g., gum base, binders, etc.). The unit weight for each lozenge was 210 mg. The pH of the lozenge was about 9.8 and remained stable. These lozenges dissolve within about 2-3 minutes following sublingual administration.

TABLE 4

Zolpidem lozenge formulation.

Material	Unit Quantity (mg)	Batch Quantity (g)
Sodium Carbonate, NF	17.000	357.000
Sodium Bicarbonate (Effer Soda)	23.000	483.000
Zolpidem Tartrate, EP	10.000	210.000
Pharmaburst B2	133.000	2793.000
Croscarmellose Sodium	10.000	210.000
Natural & Artificial Spearmint Flavor	6.500	136.500
Sucralose, NF	1.500	31.500
Silicon Dioxide, USP	5.500	115.500
Magnesium Stearate, NF	3.500	73.500

The batch quantity formulation produces 21,000 unit doses.

The zolpidem lozenge composition of the present invention can be used, e.g., for treatment of insomnia. In certain instances, after the introduction of a lozenge into the mouth, the subject holds the lozenge underneath the tongue and either swallows while the lozenge is dissolving or swallows after the lozenge has dissolved. The lozenges described herein have a very rapid rate of dissolution, and are capable of dissolving within about 2-3 minutes following sublingual administration.

A typical dosage form of the zolpidem lozenge of the present invention is designed to produce an average plasma concentration of at least from about 20 to about 300 nanograms of zolpidem per milliliter of plasma. For example, a 5 mg zolpidem lozenge can be designed to produce a mean peak plasma concentration within the range of from about 20 to about 100 nanograms of zolpidem per milliliter of plasma within about 5 minutes to about 2 hours. Similarly, a 10 mg zolpidem lozenge can be designed to produce a mean peak plasma concentration within the range of from about 100 to about 300 nanograms of zolpidem per milliliter of plasma within about 5 minutes to about 2 hours.

The lozenge compositions of the present invention provide a convenient, reliable, practical, and painless system for delivering zolpidem across the oral mucosa. Notably, the lozenge compositions are capable of very rapidly delivering zolpidem with low inter-subject variability in terms of maximum plasma concentration (C_{max}) and the time to reach the maximum plasma concentration (T_{max}) so that a therapeutically effective amount of zolpidem enters the bloodstream within about 30 minutes, 20 minutes, 15 minutes, 10 minutes, 5 minutes, or even within about 1-2 minutes after zolpidem is released from the carrier.

Example 5

Dissolution Profiles for Zolpidem Tablet and Lozenge Compositions

This example illustrates the mean dissolution profiles for a zolpidem quick-dissolving tablet made according to Table 3 and a zolpidem lozenge made according to Table 4.

The compositions tested were as follows:

1. Zolpidem quick-dissolving tablet (typically dissolves sublingually in about 5 minutes).
2. Zolpidem lozenge (typically dissolves sublingually in about 2-3 minutes).

The experimental conditions were as follows:

Method=USP
Apparatus=USP Apparatus II
Medium=Phosphate Buffer pH 6.8
Volume of the Medium=500 ml
Spindle Speed=25 rpm
Temperature=37° C.

Table 5 below shows the dissolution data and FIG. **2** shows the mean dissolution profiles for a zolpidem quick-dissolving tablet and zolpidem lozenge of the present invention at 5, 10, 15, 20, and 30 minutes in phosphate buffered medium (pH 6.8).

TABLE 5

Dissolution data for the zolpidem quick-dissolving tablet and zolpidem lozenge.

Time (Min.)	Quick-Dissolving Tablet (% Dissolved, RSD[1])	Lozenge (% Dissolved, RSD[1])
5	14.3, 17.7	32.4, 16.2
10	32.8, 14.8	61.7, 8.6
15	50.1, 14.6	75.7, 4.9
20	63, 15.9	82.1, 4.6
30	85.2, 7.9	88.6, 2.8

[1]RSD = Relative Standard Deviation

Example 6

Zolpidem Pharmacokinetic Studies

This example provides two studies illustrating the pharmacokinetic profile of the zolpidem tablets of the present invention as compared to a dose equivalent commercial oral tablet.

Zolpidem Sublingual Powdered Tablet vs. Ambien Oral Tablet:

To evaluate the pharmacokinetic profile of a sublingually administered zolpidem formulation, a 10 mg zolpidem powdered tablet buffered at a pH of 9.8 with 23 mg sodium bicarbonate and 17 mg sodium carbonate (Formulation A) was determined in eight healthy subjects (5 male, 3 female). Formulation A was administered under the subject's tongue and had a very rapid dissolution rate, i.e., within about 1 to about 3 minutes. The study performed was a fixed-sequence, open-label pharmacokinetic study in which subjects swallowed saliva at a rate of every 2, 5, or 10 minutes over a 10 minute period of time ("swallowing time"). For example, a 2 minute swallowing time refers to swallowing saliva every 2 minutes over a 10 minute period (i.e., 5 blocks of 2 minutes each); a 5 minute swallowing time refers to swallowing saliva every 5 minutes over a 10 minute period (i.e., 2 blocks of 5 minutes each); and a 10 minute swallowing time refers swallowing saliva every 10 minutes over a 10 minute period (i.e., 1 block of 10 minutes). Serum blood samples were collected over an 8 hour period and the plasma was assayed for zolpidem levels, e.g., using high pressure liquid chromatography (HPLC)-tandem mass spectrometry (MS).

FIGS. **3-5** show the plasma concentration over time in each subject for Formulation A at swallowing times of 2, 5, and 10 minutes, respectively. Tables 6-8 below show the values for the pharmacokinetic parameters determined in each subject for Formulation A at swallowing times of 2, 5, and 10 minutes, respectively.

TABLE 6

Pharmacokinetic parameters for Formulation A at a 2 minute swallowing time.

Subject	T_{max} (min.)	C_{max} (ng/ml)	AUC_{0-8} (ng · hr/ml)
1	30	142	317
2	25	231	1096
3	180	211	776
4	90	141	430
5	50	182	645
6	90	128	441
7	90	142	663
8	25	96	363
Median (Range)	70 (25-180)		
Mean (CV %)		159 (28%)	592 (44%)

TABLE 7

Pharmacokinetic parameters for Formulation A at a 5 minute swallowing time.

Subject	T_{max} (min.)	C_{max} (ng/ml)	AUC_{0-8} (ng · hr/ml)
1	30	134	350
2	25	252	1201
3	90	168	906
4	50	172	517
5	25	191	520
6	90	146	490
7	120	185	805
8	40	77	464
Median (Range)	45 (25-120)		
Mean (CV %)		165 (30%)	656 (44%)

TABLE 8

Pharmacokinetic parameters for Formulation A at a 10 minute swallowing time.

Subject	T_{max} (min.)	C_{max} (ng/ml)	AUC_{0-8} (ng · hr/ml)
1	390	137	364
2	25	241	913
3	120	183	824
4	90	120	508
5	50	196	728
6	50	208	587
7	50	131	708
8	60	158	826
Median (Range)	55 (25-120)		
Mean (CV %)		172 (28%)	682 (27%)

The pharmacokinetic results obtained for Formulation A were then compared to pharmacokinetic data obtained from the package insert and the literature for a dose equivalent Ambien® oral tablet formulation (Formulation B). FIG. **6** shows the mean plasma concentration over time for Formulation A (zolpidem sublingual powdered tablet) at the 3 different swallowing times and for Formulation B (peroral (PO) Ambien®), which was obtained from the literature (Greenblatt et al., *Clin. Pharmacol. Ther.,* 64:553-561 (1998); Greenblatt et al., *Clin. Pharmacol. Ther.,* 64:661-671 (1998)). Table 9 below shows the mean values for the pharmacokinetic parameters determined for Formulation A at the 3 different swallowing times and those for Formulation B from the literature (Greenblatt et al., *Clin. Pharmacol. Ther.,* 64:553-561 (1998)).

TABLE 9

Pharmacokinetic parameters for Formulation A and Formulation B.

Formulation	T_{max} (min.)	C_{max} (ng/ml)	AUC (ng · hr/ml)
Formulation A (2 min. swallowing time)	70 (25-180)	159 (28%)	592 (44%)
Formulation A (5 min. swallowing time)	45 (25-120)	165 (30%)	656 (44%)
Formulation A (10 min. swallowing time)	55 (25-120)	172 (24%)	682 (27%)
Formulation A (Cumulative)	55 (25-180)	166 (25%)	644 (37%)
Formulation B	102 (84-120)	125 (12%)	408 (12%)

Values represent the mean. The numbers in parentheses for T_{max} represent the minimum and maximum values, respectively. The numbers in parentheses for C_{max} and AUC represent the coefficient of variation percent (CV %).

This study demonstrates that delivery of zolpidem across the oral mucosa produced mean plasma zolpidem concentrations that were from about 45% to about 67% greater than those observed for the commercial oral tablet during the 8 hour period following administration. In addition, peak plasma zolpidem concentrations were achieved within about 45 to about 70 minutes following sublingual administration, while peak plasma zolpidem concentrations were not achieved until 96 minutes (Ambien® package insert) or 102 minutes (Greenblatt et al., *Clin. Pharmacol. Ther.,* 64:553-561 (1998)) following commercial oral tablet administration. As such, the present study shows that zolpidem from the powdered sublingual tablet is rapidly absorbed and has sub-

stantially better bioavailability than the commercial oral tablet. The present study also shows that the improvement in bioavailability is independent of the swallowing time.

FIG. **7** shows the mean plasma concentration over time for Formulation A at swallowing times of 2 and 5 minutes using the data from all 8 subjects and the mean plasma concentration over time for Formulation A at swallowing times of 2 and 5 minutes excluding the data from subjects 3, 6, and 7, who apparently swallowed earlier than their scheduled swallowing time. Table 10 below shows the mean values for the pharmacokinetic parameters determined for Formulation A using the data from all 8 subjects or excluding the data from subjects 3, 6, and 7. When subjects who apparently did not comply with the study protocol were excluded from the analysis, peak plasma zolpidem concentrations for the remaining subjects were achieved within about 30 minutes rather than from about 45 to about 70 minutes following sublingual administration.

TABLE 10

Pharmacokinetic parameters for Formulation A with all subjects or excluding those who swallowed early.

Swallowing Time	T_{max} (min.)	C_{max} (ng/ml)	AUC (ng · hr/ml)
2 minutes (all subjects)	70 (25-180)	159 (28%)	592 (44%)
2 minutes (excluding subjects 3, 6, and 7)	30 (25-90)	159 (31%)	570 (44%)
5 minutes (all subjects)	45 (25-120)	165 (30%)	656 (56%)
5 minutes (excluding subjects 3, 6, and 7)	30 (25-50)	165 (40%)	609 (55%)

Values represent the mean. The numbers in parentheses for T_{max} represent the minimum and maximum values, respectively. The numbers in parentheses for C_{max} and AUC represent the coefficient of variation percent (CV %).

FIG. **8** is an expanded view of the first 90 minutes shown in FIG. **6**. In particular, FIG. **8** illustrates the estimated time for the onset of sleep in subjects taking Formulation A (left dotted line) compared to the time for the onset of sleep in subjects taking Formulation B (right dotted line). The mean plasma zolpidem concentration effective for inducing sleep onset is shown by the horizontal line in FIG. **8**. Table 11 below shows the reported time for the onset of sleep during the daytime in each subject taking Formulation A at the 3 different swallowing times.

TABLE 11

Reported daytime sleep onset times for Formulation A.

Subject	2 min. swallowing time (min.)	5 min. swallowing time (min.)	10 min. swallowing time (min.)
1	10	16	18
2	12	9	14
3	7	7	18
4	49	19	8
5	5	19	24
6	30	19	18
7	25	23	15
8	13	24	14
Median	12.5	19	16.5

This study demonstrates that the onset of sleep for subjects taking the zolpidem powdered sublingual tablet is substantially faster than that achieved with the commercial oral tablet. In fact, the onset of sleep for subjects taking the sublingual tablets of the present invention can be as early as within about 12.5 minutes following administration, which is more than 3 times faster than the onset of sleep for subjects taking the commercial oral tablet. One skilled in the art will appreciate that the onset of sleep observed during the daytime corresponds to the onset of sleep at night.

Furthermore, the pharmacokinetic profiles for sublingually administered zolpidem provide a softer and longer-lasting peak of zolpidem (see, FIG. **6**), and thus resemble a pharmacokinetic profile for intravenously administered zolpidem. As a result, this infusion-like pharmacokinetic profile is equivalent to or even superior to the commercial oral tablet in reducing the time to onset of therapeutic activity, maintaining sleep (e.g., total sleep time, number of awakenings), enhancing sleep quality, eliminating the effect of food, and reducing any morning-after residual effects.

Zolpidem Slow-Dissolving and Quick-Dissolving Sublingual Tablets vs. Ambien Oral Tablet:

To further evaluate the pharmacokinetic profile of a sublingually administered zolpidem formulation, a 10 mg zolpidem slow-dissolving tablet made according to Table 2 (Formulation C) and a 10 mg zolpidem quick-dissolving tablet made according to Table 3 (Formulation D) was compared to a dose equivalent Ambien® oral tablet formulation (Formulation B) in eight healthy subjects. Formulation C (SL Tablet) was administered under the subject's tongue and had a slow dissolution rate, i.e., within about 10 minutes. Formulation D (FS Tablet) was administered under the subject's tongue and had a fast dissolution rate, i.e., within about 5 minutes. Formulation B (PO Ambien) was administered perorally with 180 ml of water. The study performed was a three-way crossover, fixed-sequence pharmacokinetic study in which subjects swallowed saliva at a rate of every 2 or 5 minutes over a 10 minute period of time ("swallowing time") for Formulations C and D. Serum blood samples were collected over a 12 hour period and the plasma was assayed for zolpidem levels, e.g., using high pressure liquid chromatography (HPLC)-tandem mass spectrometry (MS).

FIG. **9** shows the mean plasma concentration over time for Formulation C (SL Tablet) at swallowing times of 2 and 5 minutes and for Formulation B (PO Ambien). Likewise, FIG. **10** shows the mean plasma concentration over time for Formulation D (FS Tablet) at swallowing times of 2 and 5 minutes and for Formulation B (PO Ambien). This study demonstrates that delivery of zolpidem across the oral mucosa produced peak plasma zolpidem concentrations at a substantially earlier period in time and at a substantially higher level following sublingual administration than observed for the commercial oral tablet administration. As such, the present study shows that zolpidem from both dissolving tablets is rapidly absorbed and has substantially better bioavailability than the commercial oral tablet. Furthermore, the onset of sleep for subjects taking either zolpidem dissolving tablet is substantially faster than that achieved with the commercial oral tablet. The present study also shows that the improvement in bioavailability is independent of the swallowing time and the formulation of the dissolving tablet.

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 for treating insomnia, comprising the steps of:

administering a solid pharmaceutical composition comprising zolpidem or a pharmaceutically acceptable salt thereof to a subject prone to insomnia, the pharmaceutical composition further comprising a buffer,

wherein the buffer raises the pH of saliva to a pH of about 7.8 or greater,

wherein zolpidem is absorbed across a permeable membrane of the subject's oral mucosa, and

wherein at least 75% of the solid pharmaceutical composition dissolves within about 10 minutes or less within an oral cavity following administration.

2. The method of claim 1, wherein the solid pharmaceutical composition further comprises a binder and a disintegrating agent.

3. The method of claim 1, wherein the solid pharmaceutical composition dissolves within about 1-3 minutes within the oral cavity of the subject following administration.

4. The method of claim 1, wherein the solid pharmaceutical composition dissolves within about 2-3 minutes within the subject's oral cavity following administration.

5. The method of claim 1, wherein the solid pharmaceutical composition is administered sublingually.

6. The method of claim 1, wherein the oral mucosa is selected from the group consisting of sublingual mucosa, buccal mucosa, gingival mucosa, palatal mucosa, and lining of the lips.

7. The method of claim 1, wherein a mean peak plasma concentration of zolpidem between about 20 to about 100 ng/mL is produced within about 30 minutes.

8. The method of claim 1, wherein a therapeutically effective amount of zolpidem enters the bloodstream within about 30 minutes.

9. The method of claim 1, wherein the buffer comprises a carbonate buffer and a bicarbonate buffer.

10. The method of claim 9, wherein the carbonate buffer and bicarbonate buffer are present in a carbonate:bicarbonate weight ratio of about 1:1 to about 1:10.

11. The method of claim 1, wherein the solid pharmaceutical composition is a lozenge.

12. The method of claim 1, wherein the solid pharmaceutical composition is a tablet.

13. The method of claim 9, wherein the carbonate buffer and bicarbonate buffer are present in a carbonate:bicarbonate weight ratio of about 1:1 to about 1:5.

14. The method of claim 1, wherein an average plasma concentration is from about 20 to about 300 ng/ml.

15. The method of claim 1, wherein the zolpidem or pharmaceutically acceptable salt is zolpidem tartrate.

16. The method of claim 1, wherein the zolpidem or pharmaceutically acceptable salt thereof is in an amount from about 1 mg to about 5 mg.

17. The method of claim 1, wherein the zolpidem or pharmaceutically acceptable salt thereof is in an amount from about 2 mg to about 5 mg.

* * * * *