PRODUCT MONOGRAPH

T\C SUBLINOX®
Zolpidem tartrate
5 mg and 10 mg sublingual orally disintegrating tablets (ODT)

Hypnotic Agent

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral/sublingual	Orally Disintegrating Tablet (ODT) 5 mg, 10 mg	Colloidal Silicon Dioxide, Croscarmellose Sodium, Magnesium Stearate, Mannitol, Saccharin Sodium, Silicified Microcrystalline Cellulose

INDICATIONS AND CLINICAL USE
Since sleep disturbances may be the presenting manifestation of a physical and/or psychiatric disorder, symptomatic treatment of insomnia should be initiated only after a careful evaluation of the patient.

Adults
SUBLINOX (zolpidem tartrate ODT) is indicated for the short-term treatment and symptomatic relief of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakenings.

Treatment with SUBLINOX should usually not exceed 7 to 10 consecutive days. Use for more than 2-3 consecutive weeks requires complete re-evaluation of the patient.
Prescriptions for SUBLINOX should be written for short-term use (7-10 days) and it should not be prescribed in quantities exceeding a 1-month supply.

The use of hypnotics should be restricted for insomnia where disturbed sleep results in impaired daytime functioning.

Geriatrics (≥ 65 years of age)
Elderly patients are especially susceptible to dose-related adverse effects, such as drowsiness, dizziness, or impaired coordination. Inappropriate, heavy sedation may result in accidental events/falls. Mean C_{max}, $T_{1/2}$, and AUC were significantly increased in elderly subjects when compared to young adults. Dosage adjustments are recommended (see WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics; DOSAGE AND ADMINISTRATION, Geriatrics; ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations).

Pediatrics (< 18 years of age)
Safety and effectiveness of zolpidem in pediatric patients under the age of 18 years have not been established. Therefore, zolpidem is not recommended for use in this population (See WARNINGS AND PRECAUTIONS, Pediatrics; DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

SUBLINOX (zolpidem tartrate ODT) is contraindicated in:

- patients with known hypersensitivity to zolpidem tartrate or to any of the inactive ingredients in the formulation (see DOSAGE FORMS, COMPOSITION AND PACKAGING). Observed reactions to zolpidem tartrate–containing products include anaphylaxis and angioedema [see WARNINGS AND PRECAUTIONS].
- patients with significant obstructive sleep apnoea syndrome and acute and/or severe impairment of respiratory function.
- patients with myasthenia gravis
- patients with severe hepatic impairment
- patients with a personal or family history of sleepwalking.

WARNINGS AND PRECAUTIONS

COMPLEX SLEEP-RELATED BEHAVIOURS

Complex sleep-related behaviours 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 patients who have taken SUBLINOX. Other potentially dangerous behaviours have been reported in patients who got out of bed after taking a sedative-hypnotic and were not fully awake, including preparing and eating food, making phone calls, leaving the house, etc. As with “sleep-driving”, patients usually do not remember these events. Although complex sleep-related behaviours may occur with SUBLINOX alone at therapeutic doses, the use of alcohol and other CNS-depressants with SUBLINOX appears to increase the risk of such behaviours, as does the use of SUBLINOX at doses exceeding the maximum recommended dose.

- SUBLINOX is contraindicated in patients with a personal or family history of sleepwalking (see CONTRAINDICATIONS). Although complex-sleep behaviours have been reported in patients with or without history of sleepwalking, it is possible that some predisposed patients are at increased risk of experiencing these complex behaviours during treatment with SUBLINOX.
- SUBLINOX is not to be taken with alcohol.
- Caution is needed with concomitant use of other CNS-depressants (see DRUG INTERACTIONS).
- The use of SUBLINOX in patients with other disorders known to affect sleep and induce frequent awakenings (e.g. sleep apnea, Periodic Limb Movement Disorder, Restless Legs Syndrome) is discouraged, as they may be also at increased risk of complex sleep-related behaviours.
- Continuous use of SUBLINOX is limited to a short duration (see INDICATIONS, DOSAGE AND ADMINISTRATION).
- Patients should be instructed not to exceed the recommended dose.
- Caution should be exercised with concomitant use of potent CYP3A4 inhibitors (see DRUG INTERACTIONS).
- Due to the risk to the patient and the community, discontinuation of SUBLINOX should be strongly considered for patients who report *any* such complex sleep-related behaviours.

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 tartrate.

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

General

Benzodiazepine and benzodiazepine-like compounds should be used with extreme caution in patients with a history of substance or alcohol abuse (see WARNINGS AND PRECAUTIONS, Drug Abuse and Dependence).

SUBLINOX should be used with caution in patients who in the past manifested paradoxical reactions to alcohol and/or sedative medications (see WARNINGS AND PRECAUTIONS, Psychiatric).

As with other sedative/hypnotic drugs, SUBLINOX should be administered with caution to patients exhibiting signs or symptoms of depression (see WARNINGS AND PRECAUTIONS, Psychiatric).

Because some of the important adverse effects may be dose related, the smallest possible effective dose should be prescribed, especially for elderly patients. Inappropriate heavy sedation in the elderly may result in accidental events/falls. Therefore, the recommended SUBLINOX dosage is 5 mg once daily immediately before bedtime in this patient population. (see DOSAGE AND ADMINISTRATION, Geriatrics).

Clinical experience with zolpidem tartrate in patients with concomitant systemic illness is limited. Caution is advisable when using SUBLINOX in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

SUBLINOX should be avoided in pregnancy (see WARNINGS AND PRECAUTIONS, Special Populations).

Amnesia
Anterograde amnesia of varying severity has been reported following therapeutic doses of benzodiazepine and benzodiazepine-like hypnotics. The event is rare with zolpidem tartrate. Anterograde amnesia is a dose related phenomenon and elderly subjects may be at particular risk. Cases of transient global amnesia and "traveller's amnesia" have also been reported in association with benzodiazepines, the latter in individuals who have taken the drug often in the middle of the night, to induce sleep while traveling. Transient global amnesia and traveler's amnesia are unpredictable and not necessarily dose-related phenomena. Patients should be warned not to take SUBLINOX under circumstances in which a full night's sleep (7-8 hours) and clearance of the drug from the body are not possible before they need to resume full activity.

Abnormal Thinking and Behavioral Changes
A variety of abnormal thinking and behavior changes have been reported to occur in association with the use of sedative/hypnotics. Some of these changes may be characterized by decreased inhibition (e.g. aggressiveness and extroversion that seemed out of character), similar to effects produced by alcohol and other CNS depressants. Visual and auditory hallucinations have been reported as well as behavioral changes such as bizarre behavior, irritability, anger, nightmare, agitation and depersonalization. Other neuropsychiatric symptoms may occur unpredictably. Abnormal behaviors associated with the use of benzodiazepines or benzodiazepine-like agents have been reported more with chronic use and/or high doses but they may occur during the acute, maintenance or withdrawal phases of treatment. In controlled trials, <1% of adults with insomnia who received zolpidem tartrate reported hallucinations.

It can rarely be determined with certainty whether a particular instance of the abnormal behaviors listed above is drug-induced, spontaneous in origin, or a result of an underlying

psychiatric or physical disorder. Nonetheless, the emergence of any new behavioral sign or symptom of concern requires careful and immediate evaluation. Should these occur, use of the product should be discontinued. These reactions are more likely to occur in the elderly.

Cognitive Function
Benzodiazepines and benzodiazepine-like compounds may affect concentration, attention and vigilance. This risk is greater in the elderly and in patients with cerebral impairment.

Complex Sleep-related Behaviors
See boxed WARNINGS AND PRECAUTIONS: COMPLEX SLEEP-RELATED BEHAVIOURS.

CNS Depressant Effects and Next-Day Impairment
Like other sedative/hypnotic drugs, SUBLINOX has CNS-depressant effects. Due to the rapid onset of action, SUBLINOX should be ingested **immediately prior to going to bed**.

Patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness or motor coordination such as operating machinery or driving a motor vehicle after ingesting the drug. This includes potential impairment of the performance of such activities that may occur the day following ingestion of SUBLINOX. The risk of next day psychomotor impairment, including impaired driving, is increased if SUBLINOX is taken with less than a full night of sleep remaining (7 to 8 hours); if a higher dose than the recommended dose is taken; if co-administered with other CNS depressants; or if co-administered with other drugs that increase the blood level of zolpidem. Patients should be cautioned against taking SUBLINOX in these circumstances. The lowest effective dose for the patient should be used. SUBLINOX is ***not*** to be taken with alcohol or other sedative hypnotics (including other zolpidem products) at bedtime or the middle of the night. If concomitant use of another CNS depressant or a drug that increases zolpidem levels is clinically warranted, dosage adjustments of SUBLINOX may be necessary. Even if SUBLINOX is taken as instructed, some patients may still have zolpidem blood levels in the morning high enough to produce impairment (see DOSAGE AND ADMINISTRATION, DRUG INTERACTIONS and PATIENT COUNSELING INFORMATION

Drug Abuse and Dependence

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. Addiction is a primary, chronic, neurobiological disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving. Drug addiction is a treatable disease, using a multidisciplinary approach, but relapse is common. Studies of abuse potential in former drug abusers found that the effects of single doses of zolpidem tartrate 40 mg were similar, but not identical, to diazepam 20 mg, while zolpidem tartrate 10 mg 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 SUBLINOX, they should be monitored carefully when receiving SUBLINOX or any other hypnotic.

Tolerance
Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug effects over time. Tolerance may occur to both desired and undesired effects of drugs and may develop at different rates for different effects. Some loss of efficacy to the hypnotic effects of benzodiazepine and benzodiazepine-like agents including SUBLINOX may develop after repeated use for a few weeks

Dependence
Use of sedative/hypnotic agents like SUBLINOX may lead to the development of physical and psychological 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.

Following rapid dose decrease or abrupt discontinuation of sedative/hypnotics, there have been reports of signs and symptoms similar to those associated with withdrawal from other CNS-depressants. 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.

Other symptoms include headache, extreme anxiety and tension, restlessness, confusion and irritability. In severe cases the following symptoms may occur: derealization, depersonalization, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations and epileptic seizures.

The following possible withdrawal symptoms were reported during clinical trials following placebo substitution occurring within 48 hours following last zolpidem treatment: fatigue, nausea, flushing, lightheadedness, uncontrolled crying, emesis, stomach cramps, panic attack, nervousness, and abdominal discomfort. These reported adverse events occurred at an incidence of 1% or less. Consequently, abrupt discontinuation should be avoided and a gradual dosage-tapering schedule is recommended for patients taking the drug for more than a few weeks.

When SUBLINOX is used in accordance with the recommendations for dosage, duration of treatment and warnings, the risk of withdrawal symptoms or rebound phenomena occurring is minimal. The risk of dependence increases with dose and duration of treatment; it is also greater in patients with a history of psychiatric disorders and/or history of addiction to, or abuse of, drugs or alcohol. Tolerance, withdrawal or rebound phenomena have been observed when using SUBLINOX outside recommendations for use in these patients. As with any other hypnotic, these patients should be under careful surveillance when receiving SUBLINOX.

Rebound Insomnia
A transient syndrome whereby the symptoms that led to treatment with sedative/hypnotic agents recur in an enhanced form may occur on withdrawal of hypnotic treatment. It may be accompanied by other reactions including mood changes, anxiety and restlessness.

It is important that the patient should be aware of the possibility of rebound phenomena, thereby minimizing anxiety over such symptoms should they occur when the medicinal product is discontinued.

In the case of benzodiazepine and benzodiazepine-like agents with a short duration of action, withdrawal phenomena can become manifest within the dosage interval.

As with all hypnotics, repeat prescriptions should be limited to those who are under medical supervision.

Carcinogenesis and Mutagenesis

No evidence of carcinogenic potential was observed in mice. In rats, renal tumors (lipoma, liposarcoma) were seen at the mid- and high doses.

Zolpidem was administered to mice and rats for 2 years at dietary dosages of 4, 18, and 80 mg base/kg. In mice, these doses are ≈2.5, 10, and 50 times the maximum recommended human dose (MRHD) of 10 mg/day (8 mg zolpidem base) on mg/m^2 basis. In rats, these doses are ≈5, 20, and 100 times the MRHD on a mg/m^2 basis.

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 or ≈5, 24, and 120 times the MRHD on a mg/m^2 basis) to rats prior to and during mating, and continuing in females through postpartum day 25, resulted in irregular estrus cycles and prolonged precoital intervals. The no-effect dose for these findings is ≈24 times the MRHD on a mg/m^2 basis. There was no impairment of fertility at any dose tested.

Psychiatric

Use in patients with depression

As with other sedative/hypnotic drugs, SUBLINOX should be administered with caution to patients exhibiting signs or symptoms of depression. Suicidal tendencies may be present in such patients and protective measures may be required. Intentional over-dosage is more common in this group of patients; therefore, the least amount of drug that is feasible should be prescribed for the patient at any one time. In primarily depressed patients, worsening of depression, including suicidal thoughts and actions (including completed suicides), has been reported in association with the use of sedative/hypnotics. Pre-existing depression may be unmasked during use of SUBLINOX. Since insomnia may be a symptom of depression, the patient should be re-evaluated if insomnia persists.

Other psychiatric and paradoxical reactions/somnambulism and associated behaviours
SUBLINOX should be used with caution in patients who in the past manifested paradoxical reactions to alcohol and/or sedative medications. Paradoxical reactions like restlessness, exacerbated insomnia, insomnia, agitation, irritability, aggression, delusion, anger, nightmares, hallucinations, psychosis, or abnormal behaviors are more likely to occur in the elderly.

Psychotic illness
Hypnotics are not recommended for the primary treatment of psychotic illness.

Anxiety/Restlessness
Although not seen with SUBLINOX to date, an increase in daytime anxiety and/or restlessness has been observed during treatment with other hypnotics with a short elimination half-life. This is believed to be due to interdose withdrawal.

Respiratory

Although studies did not reveal respiratory depressant effects at hypnotic doses of zolpidem tartrate in normal 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 tartrate (10 mg) when compared to placebo. Post-marketing reports of respiratory insufficiency following treatment with zolpidem tartrate, most of which involved patients with pre-existing respiratory impairment, have been received. Since sedative/hypnotics have the capacity to depress respiratory drive, precautions should be taken if SUBLINOX is prescribed to patients with compromised respiratory function. SUBLINOX should be used with caution in patients with sleep apnea syndrome or myasthenia gravis. SUBLINOX is contraindicated in patients with acute and/or severe respiratory impairment, e.g. significant apnea syndrome (See CONTRAINDICATIONS).

Special Populations

Pregnant Women
Benzodiazepines may cause fetal damage when administered during pregnancy. During the first trimester of pregnancy, several studies have suggested an increased risk of congenital malformations associated with the use of benzodiazepines.

There are no adequate and well-controlled studies of SUBLINOX in pregnant women. SUBLINOX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. As a precautionary measure, it is preferable to avoid the use of SUBLINOX during pregnancy.

If SUBLINOX is prescribed to a woman of child-bearing potential, the patient should be warned of the potential risk to a fetus and advised to consult her physician regarding the discontinuation of the drug if she intends to become pregnant or suspects that she is pregnant.

Studies to assess the effects on children whose mothers took zolpidem during pregnancy have not been conducted. There is a published case report documenting the presence of zolpidem in human umbilical cord blood. Children born to mothers taking sedative-hypnotic drugs may be at some risk for physical dependence and withdrawal symptoms from the drug during the postnatal period. Effects on the neonate such as hypothermia and moderate respiratory depression can be expected due to the pharmacological action of the product. In addition, neonatal flaccidity has been reported in infants born to mothers who received sedative-hypnotic drugs during pregnancy.

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.

Nursing Women
Zolpidem is excreted into human milk. Studies in lactating mothers indicate that the $T_{1/2}$ of zolpidem is similar to that in non-lactating women (2.6 ± 0.3 hours). The effect of zolpidem on the nursing infant is not known. The use of SUBLINOX in nursing mothers is not recommended.

Pediatrics (< 18 years of age)
Safety and effectiveness of Zolpidem have not been established in pediatric patients below the age of 18. Therefore, zolpidem should not be prescribed in this population. In an 8-week study in pediatric patients (aged 6-17 years) with insomnia associated with attention-deficit/hyperactivity disorder (ADHD), psychiatric and nervous system disorders comprised the most frequent treatment emergent adverse events observed with zolpidem versus placebo and included dizziness (23.5% vs. 1.5%), headache (12.5% vs. 9.2%), and hallucinations (7.4% vs. 0%) (see DOSAGE AND ADMINISTRATION, Pediatrics).

Geriatrics (≥65 years of age)
Impaired motor and/or cognitive performance such as drowsiness, dizziness, or impaired coordination after exposure to usually recommended adult doses, or unusual sensitivity to sedative/hypnotic drugs is a concern in the treatment of elderly and/or debilitated patients. Inappropriate, heavy sedation may result in accidental events/falls. Mean C_{max}, $T_{1/2}$, and AUC were significantly increased in elderly subjects when compared to results in young adults. Therefore, the recommended SUBLINOX dosage is 5 mg once daily immediately before bedtime in this patient population (see DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations).

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

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

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

Hepatic Impairment
A study in subjects with hepatic impairment treated with zolpidem tartrate did reveal prolonged elimination in this group; therefore, the recommended SUBLINOX dosage is 5 mg once daily immediately before bedtime in patients with hepatic impairment and they should be closely monitored. SUBLINOX is contraindicated in patients with severe hepatic insufficiency [see CONTRAINDICATIONS, DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY].

Renal Impairment
Data in end-stage renal failure patients repeatedly treated with zolpidem tartrate did not demonstrate drug accumulation or alterations in pharmacokinetic parameters. No dosage adjustment of SUBLINOX in renally impaired patients is required; however, these patients should be closely monitored [see ACTION AND CLINICAL PHARMACOLOGY].

Gender Difference in Pharmacokinetics
Women clear zolpidem tartrate from the body at a lower rate and have higher blood levels of zolpidem compared to men. The recommended initial dose of SUBLINOX for adult women is 5 mg, and the recommended dose for adult men is 5 or 10 mg.

In geriatric patients, clearance of zolpidem is similar in men and women. The recommended dose of SUBLINOX in geriatric patients is 5 mg regardless of gender [see DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY].

PATIENT COUNSELING INFORMATION

The physician should advise the patients, their families, and their caregivers about the benefits and risks associated with treatment with sedative-hypnotics and should counsel them on its appropriate use. The physician should instruct them to read the Consumer Information Leaflet that is included in the package of SUBLINOX (zolpidem tartrate ODT) dispensed to the patient. The patient should read this leaflet very carefully before starting treatment with SUBLINOX.

Patients receiving SUBLINOX should be given the following instructions by the physician:

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

- Alcohol and other CNS-depressants should not be used by patients on SUBLINOX.
- There have been reports of people getting out of bed after taking a sedative-hypnotic and doing activities that they did not know they were doing. The next morning, they did not remember doing those activities. The activities patients may do in these situations can put them and people around them in danger. Reported activities included driving a car ("sleep-driving"), leaving the house, making and eating food, talking on the phone, etc. Patients and people close to patients should be advised to watch for this type of unusual behaviour; if they find out that the patient has done *any* such activities for which he/she has no memory they should call their doctor immediately.
- These behaviors are more likely to occur when SUBLINOX is taken with alcohol or other central nervous system-depressants or with the use of SUBLINOX at doses exceeding the maximum recommended dose.
- In addition, patients should be advised to report all concomitant medications to the prescriber.

CNS-depressant Effects and Next-Day Impairment

- Tell patients that SUBLINOX has the potential to cause next-day impairment, and that this risk is increased if dosing instructions are not carefully followed. Tell patients not to drive a car or engage in hazardous activities requiring complete alertness until they experience how the drug affects them the next day. Tell patients that if they took SUBLINOX as instructed and do not feel drowsy in the morning, they still have to wait for at least 8 hours after dosing before driving or engaging in other activities requiring full mental alertness. Inform patients that impairment can be present despite feeling fully awake.

Administration instructions

- Patients should be counseled to take SUBLINOX right before they get in bed and only when they are able to stay in bed a full night (7-8 hours) before being active again.
- SUBLINOX tablets should not be taken with or immediately after a meal.
- Advise patients NOT to take SUBLINOX when drinking alcohol, or with other CNS-depressants, including other sedative hypnotics at any time during the same night.
- SUBLINOX orally disintegrating tablets should be placed under the tongue, where it will disintegrate.
- The tablet should not be chewed or swallowed and should not be taken with water.
- Patients should be advised not to exceed the maximum recommended dose.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The following serious adverse reactions are discussed in greater detail in the WARNINGS AND PRECAUTIONS section of the Product Monograph:

- Complex Sleep-related Behaviours (see boxed Warning)
- Severe anaphylactic and anaphylactoid reactions
- Anterograde amnesia
- Abnormal Thinking and Behavioural Changes
- CNS-depressant effects
- Drug Abuse and Dependence/Withdrawal symptoms/Rebound Insomnia
- Effects on the neonate (see Pregnant Women)

Clinical Trial Adverse Drug Reactions – zolpidem tartrate oral tablets

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adverse Drug Reactions Associated with Discontinuation of Treatment – zolpidem tartrate oral tablets

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

Approximately 4% of 1,959 patients who received zolpidem tartrate at all doses (1 to 50 mg) in similar foreign trials discontinued treatment because of an adverse reaction. Reactions most commonly associated with discontinuation from these trials were daytime drowsiness (1.1%), dizziness/vertigo (0.8%), amnesia (0.5%), nausea (0.5%), headache (0.4%), and falls (0.4%).

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

Most Commonly Observed Adverse Events in Controlled Trials

During short-term treatment (up to 10 nights) with zolpidem tartrate at doses up to 10 mg, the most commonly observed adverse reactions associated with the use of zolpidem and seen at statistically significant differences from placebo-treated patients were drowsiness (reported by 2% of zolpidem patients), dizziness (1%), and diarrhea (1%). During longer-term treatment (28 to 35 nights) with zolpidem tartrate at doses up to 10 mg, the most commonly observed adverse

reactions associated with the use of zolpidem and seen at statistically significant differences from placebo-treated patients were dizziness (5%) and drugged feelings (3%).

Common Clinical Trial Adverse Drug Reactions ≥1% - zolpidem tartrate oral tablets
The following tables enumerate treatment-emergent adverse event frequencies that were observed at an incidence equal to 1% or greater among patients with insomnia who received zolpidem tartrate and at a greater incidence than placebo in U.S. placebo-controlled trials.

Table 1 was derived from a pool of 11 placebo-controlled short-term U.S. efficacy trials involving zolpidem in doses ranging from 1.25 to 20 mg. The table is limited to data from doses up to and including 10 mg, the highest dose recommended for use.

TABLE 1: Incidence of Treatment-Emergent Adverse Experiences in Placebo-Controlled Clinical Trials with zolpidem tartrate lasting up to 10 nights

Body System/ Adverse Event*	Zolpidem tartrate (≤ 10 mg) (N=685)	Placebo (N=473)
Central and Peripheral Nervous System		
Headache	7	6
Drowsiness	2	-
Dizziness	1	-
Gastrointestinal System		
Diarrhea	1	

*Reactions reported by at least 1% of patients treated with oral zolpidem and at a greater frequency than placebo.

Table 2 was derived from a pool of three placebo-controlled long-term efficacy trials involving oral zolpidem. These trials involved patients with chronic insomnia who were treated for 28 to 35 nights with zolpidem at doses of 5, 10, or 15 mg. The table is limited to data from doses up to and including 10 mg, the highest dose recommended for use. The table includes only adverse events occurring at an incidence of at least 1% for zolpidem patients and at greater frequency than in the placebo group.

TABLE 2: Incidence of Treatment-Emergent Adverse Experiences in Placebo-Controlled Clinical Trials with zolpidem tartrate lasting up to 35 nights (Percentage of patients reporting)

Body System/ Adverse Event*	Zolpidem tartrate (≤ 10 mg) (N=152)	Placebo (N=161)
Autonomic Nervous System		
Dry mouth	3	1
Body as a Whole		
Allergy	4	1
Back Pain	3	2
Influenza-like symptoms	2	-
Chest pain	1	-
Cardiovascular System		
Palpitation	2	-
Central and Peripheral Nervous System		
Drowsiness	8	5
Dizziness	5	1
Lethargy	3	1
Drugged feeling	3	-
Lightheadedness	2	1
Depression	2	1
Abnormal dreams	1	-
Amnesia	1	-
Sleep disorder	1	-
Gastrointestinal System		
Diarrhea	3	2
Abdominal pain	2	2
Constipation	2	1
Respiratory System		
Sinusitis	4	2
Pharyngitis	3	1
Skin and Appendages		
Rash	2	1

*Reactions reported by at least 1% of patients treated with oral zolpidem and at a greater frequency than placebo. Only dizziness and drugged feeling were reported with statistically significant differences

Pediatrics

Adverse Events Observed in Children with Insomnia associated with ADHD

The following table was derived from an 8-week study in pediatric patients (aged 6-17 years) with insomnia associated with attention-deficit/hyperactivity disorder (ADHD). In this study, psychiatric and nervous system disorders comprised the most frequent treatment emergent adverse events observed with zolpidem versus placebo and included dizziness (23.5% vs. 1.5%), headache (12.5% vs. 9.2%), and hallucinations (7.4% vs. 0%) (see WARNINGS AND PRECAUTIONS, Pediatrics and DOSAGE AND ADMINISTRATION, Pediatrics).

Table 3 - Incidence (%) of Treatment-Emergent Adverse Experiences (1% and higher than placebo) in a Placebo-Controlled Clinical Trials in children with insomnia associated with ADHD

Body System/ Adverse Event	Zolpidem tartrate (N=136)	Placebo (N=65)
Eye Disorders		
Diplopia	2.2	0
Gastrointestinal Disorders		
Diarrhea	2.9	1.5
Infections and infestations		
Nasopharyngitis	2.9	1.5
Gastroenteritis	2.9	0
Ear infection	1.5	0
Gastroenteritis viral	1.5	0
Meningitis viral	1.5	0
Pharyngitis streptococcal	1.5	0
Injury, Poisoning and Procedural Complications		
Fall	2.9	1.5
Excoriation	2.2	1.5
Injury	2.2	1.5
Joint sprain	1.5	0
Nervous System Disorders		
Dizziness	23.5	1.5
Headache	12.5	9.2
Drooling	1.5	0
Dysgeusia	1.5	0
Memory impairment	1.5	0
Tremor	1.5	0
Musculoskeletal and Connective Tissue Disorders		
Pain in extremity	1.5	0
Psychiatric Disorders		
Affect lability	2.9	0
Hallucination, visual	2.9	0
Anxiety	2.2	0
Hallucination	2.2	0
Hypnagogic hallucination	2.2	0
Sleep walking	2.2	0
Abnormal dreams	1.5	0
Disorientation	1.5	0
Renal and Urinary Disorders		

Body System/ Adverse Event	Zolpidem tartrate (N=136)	Placebo (N=65)
Enuresis	2.9	0

Dose Relationship for Adverse Events:
There is evidence from dose comparison trials suggesting a dose relationship for many of the adverse events associated with zolpidem use, particularly for certain CNS and gastrointestinal adverse events. Elderly patients are especially susceptible to dose-related adverse effects, such as drowsiness, dizziness, or impaired coordination.

Less Common Clinical Trial Adverse Drug Reactions < 1% - zolpidem tartrate oral tablets

Zolpidem was administered to 3,660 subjects in clinical trials throughout the U.S., Canada, and Europe. Treatment-emergent adverse events associated with clinical trial participation were recorded by clinical investigators using terminology of their own choosing.

To provide a meaningful estimate of the proportion of individuals experiencing treatment-emergent adverse events, similar types of untoward events were grouped into a smaller number of standardized event categories and classified utilizing a modified World Health Organization (WHO) dictionary of preferred terms.

The frequencies presented, therefore, represent the proportions of the 3,660 individuals exposed to zolpidem, at all doses, who experienced an event of the type cited on at least one occasion while receiving zolpidem.

All reported treatment-emergent adverse events are included, except those already listed in the table above of adverse events in placebo-controlled studies, those coding terms that are so general as to be uninformative, and those events where a drug cause was remote. It is important to emphasize that, although the events reported did occur during treatment with zolpidem, they were not necessarily caused by it.

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

Autonomic nervous system
Infrequent: increased sweating, pallor, postural hypotension, syncope.
Rare: abnormal accommodation, altered saliva, flushing, glaucoma, hypotension, impotence, increased saliva, tenesmus.

Body as a whole
Frequent: asthenia, fatigue.
Infrequent: edema, falling, fever, malaise, trauma.

Rare: allergic reaction, allergy aggravated, anaphylactic shock, face edema, hot flashes, increased ESR, pain, restless legs, rigors, tolerance increased, weight decrease.

Cardiovascular system*:*
Infrequent: cerebrovascular disorder, hypertension, tachycardia.
Rare: angina pectoris, arrhythmia, arteritis, circulatory failure, extrasystoles, hypertension aggravated, myocardial infarction, phlebitis, pulmonary embolism, pulmonary edema, varicose veins, ventricular tachycardia.

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

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

Hematologic and lymphatic system*:*
Rare: anemia, hyperhemoglobinemia, leukopenia, lymphadenopathy, macrocytic anemia, purpura, thrombosis.

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

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

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

Musculoskeletal system*:*
Frequent: arthralgia, myalgia.
Infrequent: arthritis.
Rare: arthrosis, muscle weakness, sciatica, tendinitis.

***Reproductive system**:*
Infrequent: menstrual disorder, vaginitis.
Rare: breast fibroadenosis, breast neoplasm, breast pain.

Respiratory system:
Frequent: rhinitis, upper respiratory infection.
Infrequent: bronchitis, coughing, dyspnea.
Rare: rhinitis, bronchospasm, epistaxis, hypoxia, laryngitis, pneumonia.

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

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

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

Clinical Trial Adverse Drug Reactions – zolpidem orally disintegrating tablets (ODT)

Two clinical studies in insomnia patients have been conducted with zolpidem orally disintegrating tablets (ODT). A total of 73 patients received single doses of zolpidem tartrate ODT (OX22) in one sleep laboratory clinical study and 60 patients received repeat doses of SUBLINOX over a maximum treatment duration of two months in an open-label study designed to evaluate tolerance in the sublingual mucosa.

Four (4) patients discontinued treatment with zolpidem ODT due to an adverse event (probably or possibly related).The events for the respective patients were 1) headache, 2) vertigo and disorientation, 3) hallucinations, somnolence, balance disorder and nausea, 4) fatigue and palpitations.

The frequencies and types of reported AEs were similar for zolpidem ODT and oral tablets in the double-blind study.

In the study designed to assess oral tissue-related adverse reactions to SUBLINOX, one patient developed transient sublingual erythema, and another transient paresthesia of the tongue. Two patients experienced treatment-emergent parasomnia in this trial (see boxed WARNING: COMPLEX SLEEP-RELATED BEHAVIOURS).

Post-Market Adverse Drug Reactions

Because reports are voluntary from a population of unknown size, an estimate of frequency cannot be made, as well, the existence of underlying medical conditions confounds the assessment of causality.

Post-market reports of skin reactions have been reported, such as angioneurotic oedema, rash, urticaria, pruritus, and hyperhidrosis.

Cases of depressed level of consciousness have been reported, mainly in the context of a drug overdose or misuse, including high doses in elderly patients (10 mg), and also with zolpidem taken at recommended doses, mostly with concomitant CNS-depressants or CYP3A4 inhibitors or substrates. A few cases of depressed level of consciousness were reported in patients taking zolpidem alone at recommended doses.

DRUG INTERACTIONS

Alcohol

Concomitant intake of SUBLINOX (zolpidem tartrate ODT) with alcohol is not recommended (see boxed warning Complex Sleep-related Behaviours). The sedative effect may be enhanced when the product is used in combination with alcohol (see WARNINGS AND PRECAUTIONS, CNS Depressant Effects).

Drug-Drug Interactions

CNS-active substances and medications

Any drug with CNS-depressant effects could potentially enhance the CNS-depressant effects of zolpidem. Therefore careful consideration should be given to the pharmacology of any CNS-active substance and medication to be used with SUBLINOX (zolpidem tartrate ODT).

SUBLINOX may produce additive CNS-depressant effects when co-administered with sedative antihistamines, anticonvulsants, narcotic analgesics, anesthetics or psychotropic medications (as antipsychotics (neuroleptics), hypnotics, anxiolytics, sedatives and antidepressant agents) which themselves produce CNS depression. However, in the case of SSRI antidepressant agents (fluoxetine and sertraline), no clinical significant pharmacokinetic or pharmacodynamic interactions have been observed. In the case of narcotic analgesics enhancement of euphoria may also occur leading to an increase in psychological dependence.

Imipramine in combination with zolpidem produced an additive effect of decreased alertness. Similarly, chlorpromazine in combination with zolpidem produced an additive effect of decreased alertness and psychomotor performance. These drugs did not show any significant pharmacokinetic interaction.

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 a lack following chronic administration.

Concomitant administration of zolpidem and sertraline increased zolpidem C_{max} (43%) and decreased T_{max} (53%), whether or not these changes alter the pharmacodynamic effect of zolpidem is unknown.

Drugs that affect drug metabolism via cytochrome P450
Some compounds known to potently inhibit or induce cytochrome P450 CYP3A were shown to increase or reduce exposure to zolpidem.

A randomized, double-blind, crossover interaction study in ten healthy volunteers between itraconazole (200 mg once daily for 4 days) and a single dose of zolpidem (10 mg) given 5 hours after the last dose of itraconazole resulted in a 34% increase in AUC 0-∞ of zolpidem.

Co-administration of a single dose of zolpidem tartrate with 4 doses of ketoconazole, a potent CYP3A4 inhibitor 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.

Caution should be exercised and consideration should be given to using a lower dose of zolpidem when ketoconazole or other potent CYP3A inhibitors and zolpidem are given together. Patients should be advised that use of SUBLINOX (zolpidem tartrate sublingual tablets) with ketoconazole or other potent CYP3A inhibitors may enhance sedation and other effects of the drug (see boxed warning Complex Sleep-related Behaviours).

Co-administration of multiple doses of rifampin and a single dose of zolpidem tartrate (20 mg) given 17 hours after the last dose of rifampin showed significant reductions of the AUC (73%), C_{max} (58%), and $T_{1/2}$ (36%) of zolpidem together with significant reductions in the pharmacodynamic effects of zolpidem tartrate, suggesting that rifampin or other potent inducers of CYP3A may substantially affect the pharmacodynamic response to zolpidem.

The effect of inhibitors of other P450 enzymes has not been carefully evaluated.

Drug-Food Interactions

SUBLINOX should not be administered with or immediately after a meal. Concomitant food intake vs fasted state results in significantly reduced rate and extent of absorption (C_{max} and AUC reduced by about 30 % and 20% respectively) and also delayed absorption (median T_{max} fed vs. fasted = 105 vs 82 minutes).

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

DOSAGE AND ADMINISTRATION

Dosing Considerations

As with all hypnotics, long-term use of SUBLINOX is not recommended. Treatment with SUBLINOX (zolpidem tartrate ODT) should usually not exceed 7-10 consecutive days. Use for more than 2-3 consecutive weeks requires complete re-evaluation of the patient.

Use the lowest effective dose of SUBLINOX (zolpidem tartrate ODT) for the patient.

The effect of SUBLINOX may be slowed by ingestion with or immediately after a meal. For earlier sleep onset, SUBLINOX should not be given with or immediately after a meal.

Recommended Dose and Dosage Adjustment

Dosage in adults
The recommended initial dose is 5 mg for women and either 5 or 10 mg for men, taken only once per night immediately before bedtime with at least 7-8 hours remaining before the planned time of awakening. If the 5 mg dose is not effective, the dose can be increased to 10 mg. In some patients, the higher morning blood levels following use of the 10 mg dose increase the risk of next day impairment of driving and other activities that require full alertness (see WARNINGS AND PRECAUTIONS, CNS Depressant Effects and Next-day Impairment).

The total dose of SUBLINOX should not exceed 10 mg once daily immediately before bedtime.

The recommended initial doses for women and men are different because zolpidem clearance is lower in women (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations).

Special Populations

Pediatrics (< 18 years of age)
Safety and effectiveness of SUBLINOX in pediatric patients under the age of 18 years have not been established. Therefore, SUBLINOX should not be prescribed in this population (see WARNINGS AND PRECAUTIONS, Pediatrics).

Geriatrics (≥ 65 years of age)
Elderly or debilitated patients may be especially sensitive to the effects of zolpidem tartrate. Mean C_{max}, $T_{1/2}$, and AUC were significantly increased in elderly subjects when compared to young adults. In geriatric patients, clearance of zolpidem is similar in men and women (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations).
The recommended dose of SUBLINOX in these patients is 5 mg once daily immediately before bedtime, regardless of gender (see WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics).

Hepatic impairment
Patients with hepatic impairment do not clear the drug as rapidly as normal subjects. The recommended dose of SUBLINOX is 5 mg once daily immediately before bedtime in patients with mild to moderate hepatic impairment, with particular caution being exercised in elderly patients. SUBLINOX is contraindicated in severe hepatic impairment (See CONTRAINDICATIONS)

Use with CNS-depressants
Dosage adjustment may be necessary when SUBLINOX is combined with other CNS-depressants because of the potentially additive effects (see DRUG INTERACTIONS).

Use with potent CYP3A4 inhibitors
Consideration should be given to using a lower dose of zolpidem when ketoconazole or other potent CYP3A inhibitors and SUBLINOX are given together (see DRUG INTERACTIONS).

Administration

SUBLINOX tablet should be placed under the tongue, where it will disintegrate. The tablet should not be chewed or swallowed and should not be taken with water. Patients should be instructed to take SUBLINOX immediately prior to getting in bed, and *not* to take it in the middle of the night or at any time other than at bedtime. SUBLINOX should not be given with or immediately after a meal.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Signs and symptoms
In post-marketing experience of overdose with 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.

Recommended treatment
Based on data obtained for zolpidem tartrate, general symptomatic and supportive measures for overdose with SUBLINOX (zolpidem tartrate sublingual tablets) should be used along with immediate gastric lavage and administration of charcoal for the attenuation of drug absorption where appropriate. Intravenous fluids should be administered as needed. Zolpidem's sedative/hypnotic effect was shown to be reduced by flumazenil and therefore 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 vital signs should be monitored and general supportive measures employed. Hypotension and CNS depression should be monitored and treated by appropriate medical intervention. Sedating drugs should be withheld following zolpidem overdosage, even if excitation occurs. The value of dialysis in the treatment of overdosage has not been determined,

although hemodialysis studies in patients with renal failure receiving therapeutic doses have demonstrated that zolpidem is not dialyzable.

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

ACTION AND CLINICAL PHARMACOLOGY

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 receptor complex and shares some of the pharmacological properties of the benzodiazepines. In contrast to the benzodiazepines, which non-selectively bind to and activate all BZ receptor subtypes, zolpidem *in vitro* binds the BZ_1 receptor preferentially with a high affinity ratio of the α_1/α_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 tartrate at hypnotic doses. The (ω_1) receptor is found primarily on the Lamina IV of the sensorimotor cortical regions, substantia nigra (pars reticulate), cerebellum molecular layer, olfactory bulb, ventral thalamic complex, pons, inferior colliculus, and globus pallidus.

Pharmacodynamics

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

Pharmacokinetics

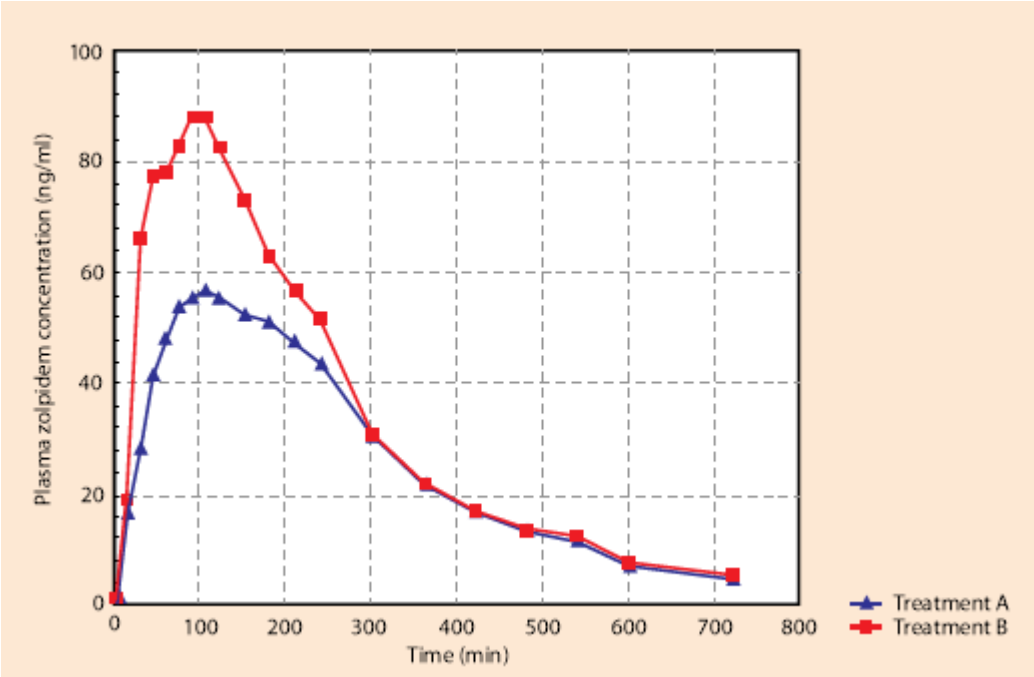
Absorption

Zolpidem tartrate ODT showed bioequivalence to zolpidem tartrate oral tablets with respect to C_{max} and AUC. Similar to zolpidem tartrate oral tablets, SUBLINOX sublingual tablets result in a pharmacokinetic profile characterized by rapid absorption.

Following administration of single 10 mg SUBLINOX, in 18 (18-65 years of age) healthy adult subjects, the mean peak concentration (C_{max}) of zolpidem was 106 ng/mL (range: 52 to 205 ng/ml) occurring at a median time (T_{max}) of 82 minutes (range: 30-180 min).

A food-effect study in 18 healthy volunteers compared the pharmacokinetics of SUBLINOX 10 mg when administered while fasting or within 20 minutes after a high fat meal. The mean AUC

and C_{max} were decreased by about 20% and 30%, respectively, while median T_{max} was prolonged by 30% (from 82 to 105 min). The half-life remained unchanged. SUBLINOX should not be administered with or immediately after a meal.



(A = SUBLINOX with food, B = SUBLINOX fasted)

Figure # 1: Mean plasma concentration - time curves following single sublingual doses of SUBLINOX administered to healthy subjects.

Distribution

Based on data obtained with oral zolpidem, the total protein binding was found to be 92.5 ± 0.1% and remained constant, independent of concentration between 40 and 790 ng/mL.

Metabolism

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

Elimination

When SUBLINOX was administered as a single 5 or 10 mg dose in healthy adult subjects, the mean zolpidem elimination half-life was 2.85 hours (range: 1.57 to 6.73 hr) and 2.65 hours (range: 1.75 to 3.77 hr) respectively.

Special Populations

Elderly

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

Gender Difference in Pharmacokinetics

Women clear zolpidem tartrate from the body at a lower rate than men, Cmax 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 initial dose of SUBLINOX for adult women is 5 mg, and the recommended dose for adult men is 5 or 10 mg.

In geriatric patients, clearance of zolpidem is similar in men and women. The recommended dose of SUBLINOX in geriatric patients is 5 mg regardless of gender.

Hepatic Impairment

The pharmacokinetics of zolpidem tartrate in eight patients with chronic hepatic impairment were compared to results in healthy subjects. Following a single 20-mg oral zolpidem tartrate dose, mean C_{max} and AUC were found to be two times (250 vs. 499 ng/mL) and five times (788 vs. 4,203 ng·hr/mL) higher, respectively, in hepatically-compromised patients while 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 healthy adult subjects of 2.2 hr (range: 1.6 to 2.4 hr). Dosage should begin at 5 mg in patients with mild to moderate hepatic impairment, with particular caution being exercised in elderly patients. In adults (under 65 years) dosage may be increased to 10 mg only where the clinical response is inadequate and the drug is well tolerated. SUBLINOX has not been studied in patients with severe hepatic insufficiency [see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION].

Renal Impairment

The pharmacokinetics of zolpidem tartrate were studied in 11 patients with end-stage 4 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. On day 1, C_{max} was 172 ± 29 ng/mL (range: 46 to 344 ng/mL). After repeated dosing for 14 or 21 days, C_{max} was 203 ± 32 ng/mL (range: 28 to 316 ng/mL). On day 1, T_{max} was 1.7 ± 0.3 hr (range: 0.5 to 3.0 hr); after repeated dosing T_{max} was 0.8 ± 0.2 hr (range: 0.5 to 2.0 hr). This variation is accounted for by noting that last-day serum sampling began 10 hours after the previous dose, rather than after

24 hours. This resulted in residual drug concentration and a shorter period to reach maximal serum concentration. On day 1, $T_{1/2}$ was 2.4 ± 0.4 hr (range: 0.4 to 5.1 hr). After repeated dosing, $T_{1/2}$ was 2.5 ± 0.4 hr (range: 0.7 to 4.2 hr). AUC was 796 ± 159 ng·hr/mL after the first dose and 818 ± 170 ng·hr/mL after repeated dosing. Zolpidem was not hemodialyzable. No accumulation of unchanged drug appeared after 14 or 21 days. Zolpidem pharmacokinetics were not significantly different in renally-impaired patients. No dosage adjustment of SUBLINOX is necessary in patients with compromised renal function. As a general precaution, these patients should be closely monitored.

STORAGE AND STABILITY

Store at controlled room temperature 15-30ºC (59-86°F). Protect from light and moisture.

SPECIAL HANDLING INSTRUCTIONS

Patients and their caregivers must be instructed to keep this medication out of reach of children and pets.

DOSAGE FORMS, COMPOSITION AND PACKAGING

SUBLINOX (zolpidem tartrate ODT) is supplied as orally disintegrating tablets for sublingual administration in two dosage strengths. Tablets are not scored.

SUBLINOX 5 mg sublingual tablets are round white tablets, flat-faced, bevel-edged with debossed "V" on one side and are supplied as a blister pack of 30 tablets.

SUBLINOX 10 mg sublingual tablets are round white tablets, flat-faced, bevel-edged with debossed "X" on one side and are supplied as a blister pack of 30 tablets.

The blister packs consist of aluminum/aluminum.

Composition

Each SUBLINOX tablet includes the following inactive ingredients: Colloidal silicon dioxide, Croscarmellose sodium, Magnesium stearate, Mannitol, Saccharin sodium, Silicified microcrystalline cellulose.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

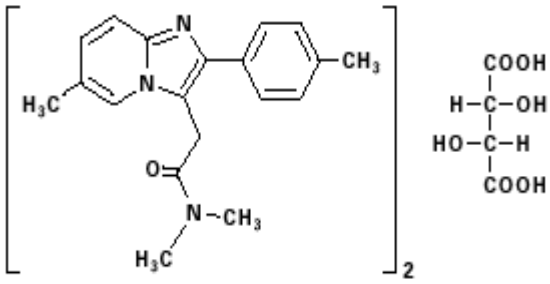
Proper name: zolpidem tartrate

Chemical name: Bis[N,N-dimethyl-2-[6-methyl-2-(4-methylphenyl)imidazo[1,2-a]pyridin-3-yl]acetamide] (2R,3R)-2,3-dihydroxybutanedioate

Molecular formula: $(C_{19}H_{21}N_3O)_2$-$C_4H_6O_6$ or $C_{42}H_{48}N_6O_8$

Molecular weight: 764.88 g/mol

Structural formula:



Physicochemical properties

Description: Zolpidem tartrate is a white to off-white crystalline powder that is sparingly soluble in water, alcohol, and propylene glycol.

CLINICAL TRIALS

Most of the efficacy data for zolpidem tartrate originated from the clinical studies performed with oral zolpidem, described below, followed by a brief description of the clinical development program for SUBLINOX ODT.

Studies with Zolpidem Tartrate Oral Tablets

Chronic Insomnia
Zolpidem was evaluated in two controlled studies for the treatment of patients with chronic insomnia (most closely resembling primary insomnia, as defined in the APA Diagnostic and Statistical Manual of Mental Disorders, DSM-IV™). Adult outpatients with chronic insomnia (n= 75) were evaluated in a double-blind, parallel group, 5-week trial comparing two doses of zolpidem tartrate and placebo. On objective (polysomnographic) measures of sleep latency and sleep efficiency, zolpidem 10 mg was superior to placebo on sleep latency for the first 4 weeks and on sleep efficiency for weeks 2 and 4. Zolpidem was comparable to placebo on number of awakenings at both doses studied.

Adult outpatients (n=141) with chronic insomnia were also evaluated, in a double-blind, parallel group, 4-week trial comparing two doses of zolpidem and placebo. Zolpidem 10 mg was superior to placebo on a subjective measure of sleep latency for all 4 weeks, and on subjective measures of total sleep time, number of awakenings, and sleep quality for the first treatment week.

Transient insomnia
Based on data obtained with zolpidem tartrate, normal adults experiencing transient insomnia (n = 462) during the first night in a sleep laboratory were evaluated in a double-blind, parallel group, single-night trial comparing two doses of zolpidem tartrate oral tablets (7.5 and 10 mg) and placebo. Both zolpidem doses were superior to placebo on objective (polysomnographic) measures of sleep latency, sleep duration, and number of awakenings.

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

Studies Pertinent To Safety Concerns for Sedative/Hypnotic Drugs

Next-day residual effects
Next-day residual effects of zolpidem tartrate were evaluated in seven studies involving normal subjects. In three studies in adults (including one study in a phase advance model of transient insomnia) and in one study in elderly subjects, a small but statistically significant decrease in performance was observed in the Digit Symbol Substitution Test (DSST) when compared placebo. Studies of zolpidem tartrate in non-elderly patients with insomnia did not detect

evidence of next-day residual effects using the DSST, the Multiple Sleep Latency Test (MSLT), and patient ratings of alertness.

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

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

Effects on sleep

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

Clinical Development Program for SUBLINOX ODT
Pharmacokinetic studies showing bioequivalence to oral zolpidem and one clinical study in insomnia patients provide data to support that the efficacy of SUBLINOX is comparable to that of oral zolpidem tartrate.

Study OX22-006 - SUBLINOX (zolpidem tartrate ODT)

The pharmacodynamic effects of zolpidem tartrate ODT were evaluated by polysomnography (PSG) in a multicenter, double-blind, randomized, active-control, single-dose, two-period crossover study in 73 patients (18-64 years of age) with primary insomnia lasting for 3 months or longer (as defined in the APA Diagnostic and Statistical Manual of Mental Disorders, DSM IV). The primary endpoint was the Latency to Persistent Sleep (LPS).

The results of this study showed that a single dose of zolpidem tartrate ODT was statistically significantly superior to zolpidem tartrate oral tablets in the mean LPS (latency to persistent sleep). The mean time to fall asleep was approximately 20 min with zolpidem tartrate ODT (10 mg) and 30 min with zolpidem tartrate oral tablets, compared to 84 min at baseline. Secondary endpoints on sleep initiation were supportive of the primary endpoint (Sleep Onset Latency and Latency to Stage 1). The exact difference in onset of sleep between the two formulations could not be established in this study because the oral zolpidem tablets were over-

encapsulated for blinding purposes, while the orally disintegrating tablets could not be over-encapsulated. The clinical effects of the encapsulation of the oral zolpidem tablets are not known. Secondary outcomes on sleep maintenance did not differ significantly between zolpidem tartrate ODT and oral zolpidem.

Table 4: OX22-006 – Latency to Persistent Sleep (LPS)

	Baseline	**SUBLINOX ODT 10 mg** (mean ± SD)	**Zolpidem tartrate oral tablets 10mg** (mean ± SD)	**Treatment Differences**	
				(Estimates ± SE)	(p value)
Primary Endpoint					
LPS (min)	84.54 ± 40.35	19.8 ± 15.5	30.1 ± 23.5	-10.3 ± 3.0	0.0010

DETAILED PHARMACOLOGY

In vitro

Zolpidem is an imidazopyridine whose mechanism and site of action have been established in rodent studies. Zolpidem differs from benzodiazepine hypnotics in that it shows a high affinity for the central BZD_1 ($omega_1$) receptor subtype with no affinity for central BZD_2 ($omega_2$) receptor subtype.

It is four times more potent in inhibiting the binding of labelled diazepam at cerebellar sites than at hippocampal sites. Labelled zolpidem shows preferential binding for BZD_1 receptors in the substantia nigra, the ventral pallidum, the cerebral cortex and the cerebellum.

Concentrations are negligible in areas rich in BZD_2 receptors, such as the striatum, nucleus accubens and dentate gyrus, and no binding is seen in the spinal cord. Like diazepam, zolpidem binding is increased by GABA and by the presence of chloride ions. At hypnotic doses, zolpidem does not significantly alter cerebral noradrenaline metabolism in the rat; it decreases cerebellar cGMP levels, but this effect is of short duration.

In vivo: Zolpidem also shows anticonvulsant, anxiolytic and muscle relaxant activity in several models, but only at doses above those that are hypnotic.

Zolpidem induces slow wave sleep in the immobilized rat at doses of 0.1 - 1.0 mg/kg i.p. or p.o. This activity appears rapidly and disappears after a brief period. There is no evidence of the development of tolerance during administration for up to eight days. Administration of benzodiazepine hypnotics in the immobilized cat ordinarily will induce a predominantly rapid EEG rhythm. Zolpidem caused less disruption of the normal pattern and produced deep sleep at doses of 0.1 - 10 mg/kg i.v., in relation to five such drugs to which it was compared. In the anesthetized monkey, doses of 0.3 - 3 mg/kg i.v. accentuate the presence of slow waves in cortical recordings.

In the freely moving implanted rat, zolpidem exhibits the effects of a rapidly acting hypnotic in recordings made during the period of light and during the period of darkness or following pCPA pre-treatment. Doses of 0.3 - 3 mg/kg p.o. increased both classical sleep and paradoxical sleep. The duration of action ranged between one and three hours; in this model midazolam's effect lasts four hours. Neither drug showed a sedative effect 24 hours after administration, and an increase in arousal was noted in the animals treated with zolpidem at this point.

In the freely moving implanted cat, zolpidem induces a short period of agitation following a dose of 1 mg/kg p.o. similar to that seen following benzodiazepine administration, but the total duration of the sleep phases and the duration of paradoxical sleep are not changed. Doses of 3 and 10 mg/kg p.o. (15-50 X HTD) increase the total time of wakefulness in the cat. Rebound insomnia was seen following triazolam after 24 hours, but not with zolpidem, which appears to cause less agitation than the benzodiazepines and does not induce rapid cortical rhythms.

In effects on motor activity, zolpidem is equal in potency to midazolam. Zolpidem is less active in decreasing muscle strength than triazolam or midazolam. Midazolam is six times more potent than zolpidem in causing motor incoordination. In effects on spinal reflexes, triazolam is eighty times (and diazepam four or five times) more potent than zolpidem. Zolpidem i.p. decreases the acquisition of conditioned fear in the mouse, but oral dosing produces no effect.

In rats trained to discriminate between chlordiazepoxide and saline (i.p.), zolpidem generally triggered the same response as saline. In discriminant tests in monkeys, zolpidem ranks below chlordiazepoxide and equal to saline. Zolpidem discrimination appears to be correlated with sedation.

Dependence potential has been studied in two models in the cynomolgus monkey. Monkeys were examined for signs of the abstinence syndrome after two weeks at 10 and two weeks at 20 mg/kg p.o. twice daily. After a week off the drug (week 5), zolpidem was reintroduced at 20 mg/kg twice daily during the sixth to ninth weeks, and evidence of an abstinence syndrome was sought during the tenth week off drug. These doses induced mild behavioural depressant effects. To obtain an equivalent effect at the beginning and end of the experiment, the zolpidem dose had to be doubled whereas that of triazolam had to be increased twenty-fold. In the second model, monkeys could self-administer intragastric doses of zolpidem by pressing a lever. It was concluded that zolpidem causes a slight abstinence syndrome and induces slight self-administration behaviour with a high degree of variability between animals tested.

Zolpidem 50 mg/kg p.o. does not alter blood pressure or baseline heart rate in the anesthetized normotensive rat. In the pithed normotensive rat, zolpidem does not interact with the alpha- or beta-adrenoceptors, or with serotonergic or muscarinic receptors. Zolpidem i.v. produced bradycardia and severe sedation in the conscious rabbit. In the anesthetized dog with a denervated heart, doses up to 0.3 mg/kg i.v. do not cause any significant change in various hemodynamic measures. At 3 mg/kg i.v., zolpidem reduces aortic pressure in dogs with neurologically normal hearts, and the bradycardia observed at lower doses is replaced by reflex tachycardia. Coronary output decreased in three of five dogs after these doses.

Zolpidem shows major peripheral analgesic activity in the acetic acid test in the mouse, but its activity in the hotplate test is very slight. Its anti-inflammatory activity is equal to that of ibuprofen. In the rat, zolpidem exhibits no platelet antiaggregant activity. In an in vitro test on rabbit platelets versus collagen, the activity of zolpidem is one-half that of aspirin and equals that of dipyridamole.

In the urethane-anesthetized rat, zolpidem 10 mg/kg i.v. does not cause any significant change in respiratory rate, respiratory minute flow volume or pulmonary resistance.

TOXICOLOGY

Local Tolerance
The local effects of zolpidem on cheek pouches were evaluated in hamsters. The histological examination showed no differences in irritation indices between SUBLINOX treated and placebo pouches or between placebo and the control pouches.

Other Toxicity Studies
Zolpidem accidently ingested by dogs up to 21 mg/kg did not induce any mortality.

Carcinogenesis, mutagenesis, impairment of fertility

Carcinogenesis
Zolpidem was administered to mice and rats for 2 years at dietary dosages of 4, 18, and 80 mg base/kg. In mice, these doses are ≈2.5, 10, and 50 times the maximum recommended human dose (MRHD) of 10 mg/day (8 mg zolpidem base) on mg/m^2 basis. In rats, these doses are ≈5, 20, and 100 times the MRHD 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 or ≈5, 24, and 120 times the MRHD on a mg/m^2 basis) to rats prior to and during mating, and continuing in females through postpartum day 25, resulted in irregular estrus cycles and prolonged precoital intervals. The no-effect dose for these findings is ≈24 times the MRHD on a mg/m^2 basis. There was no impairment of fertility at any dose tested.

Teratogenicity
When zolpidem was administered at oral doses of 4, 20, and 100 mg base/kg (approximately 5, 24, and 120 times the MRHD on a mg/m^2 basis) to pregnant rats during the period of organogenesis, dose-related decreases in fetal skull ossification occurred at all but the lowest dose, which is approximately 5 times the MRHD on a mg/m^2 basis. In rabbits treated during organogenesis with zolpidem at oral doses of 1, 4, and 16 mg base/kg (approximately 2.5, 10,

and 40 times the MRHD on a mg/m^2 basis), increased embryo-fetal death and incomplete fetal skeletal ossification occurred at the highest dose. The no-effect dose for embryo-fetal toxicity in rabbits is approximately 10 times the MRHD on a mg/m^2 basis. Administration of zolpidem to rats at oral doses of 4, 20, and 100 mg base/kg (approximately 5, 24, and 120 times the MRHD on a mg/m^2 basis) during the latter part of pregnancy and throughout lactation produced decreased offspring growth and survival at all but the lowest dose, which is approximately 5 times the MRHD on a mg/m^2 basis.

Table 1: Acute Toxicity

Species/ Route	LD_{60} mg/kg	Signs of Toxicity
Mouse p.o.	2160 (1614 - 2786) m 2320 (1622-3318) f	Deaths 3-24 hr., hypomotility, ataxia, ptosis, dyspnea, bradypnea, apnea, cyanosis, clonic convulsion.
Mouse i.p.	472 (403-552) m 444 (386-510) f	Hypomotility, prostration, tremors, startle reactions, polypnea, apnea, dyspnea, cyanosis.
Mouse i.v.	100 (83-115) m 128 (114-145) f	Sleep lethargy, piloerection, tremors, slight sporadic clonic convulsions.
Rat p.o.	556 (456 - 678) m 824 (710-956) f	Ataxia, ptosis, prostration, sleep, lacrymation, polypnea, dyspnea, startle reactions, chewing
Rat i.p.	488 (428-556) m 464 (422-510) f	Ataxia, lacrymation, polypnea, dyspnea, apnea, lethargy.
Rat i.v.	70 (66-75) m 96 (72-129) f	Sleep, prostration, jerks, Piloerection, chewing in females.

Table 2: Long-term Toxicity

Species/Route		Dosage mg/kg/day	Signs of Toxicity
Rat p.o. 1 week	(m,f)	500, 1000	Narcosis, sedation, chewing, ptosis, sialorrhea, piloerection
Rat p.o. 4 weeks	(m,f)	10, 50, 200	Sedation and hypotonia preceded by hyperactivity. At 50 and 200 mg also respiratory difficulties, chewing movement, increased thyroid, liver, kidney, ovary and adrenal weights. Decreased weight gain and food consumption. Increased urine and reticulocytes in high-dose females.
Rat p.o. 13 weeks and 4 week	(m,f)	5, 25, 125	5 mortalities at 125 mg, 1 mortality at 25 mg. Hypomotility, prostration, drowsiness,

Species/Route		Dosage mg/kg/day	Signs of Toxicity
reversibilty			hypersalivation, stereotyped movements, somnolence. Decreased weight gain and food consumption. Reversible increased liver weights in high-dose males and females.
Rat p.o. 52 weeks	(m,f)	5, 25, 125	Mortalities: 3 at 5 mg, 5 at 25 mg and 12 at 125 mg. Transient collapsed posture, unsteady gait. Weight gain decreased in males at 25 and 125 mg, and in females at 25 mg increased in females at 125 mg. Food intake increased. At 125 mg: lower RBC counts for males, decreased Hb for females, increased cholesterol and urine voided in females, increased adrenal and liver weights: enlarged adrenals in 6 females; increased incidences of basophilic hepatocytes in females.
Monkey p.o. 9 days	(m,f)	50, 75,100,150, 200	Signs reflective of pharmacologic action of drug, motor incoordination, sleep-like state, awareness retained but cutaneous sensitivity lost.
Monkey p.o. 4 weeks	(m,f)	5, 30, 180	Dose dependent sedation leading to narcosis in the high dose
Monkey p.o. 13 weeks	(m,f)	5, 25,125	Dose dependent ptosis of upper eyelid, somnolence, incoordination, body tremor, jerky body movements. Transient reduced RBC values at highest dose weeks 6 and 12.
Monkey 52 weeks	(m.f)	5, 25,125	Dose dependent subdued behaviour, ptosis, limb tremors, prostration. Increased mean body weights for males at 25 and 125 mg. Increased pituitary weights at interim sacrifice only at high dose; changes no longer apparent at termination.

Table 3: Carcinogenicity

Species/Route	Dosage mg/kg/day	Signs of Toxicity
Mouse, diet 104 weeks	4, 18, 80	Percent Survival Rates: 4 mg: Males 38. Females 48. 18 mg: Males 23. Females 50. 80 mg: Males 29, Females 65 Increased mean WBC count in high dose males due to one mouse with high lymphocyte and neutrophil counts. Age related increases in RBC abnormalities at high dose. Greater incidence of ovarian cysts at high dose. Non-neoplastic finding: increase lipid deposition in liver, at high dose higher incidence, of dilated ovarian lumen, cystic endometrial glands and ovarian cysts. No evidence of carcinogenicity.
Rat, diet 104 weeks M 109 weeks F	4, 18, 80	Percent Survival Rates: 4 mg: Males 32; Females 22 18 mg: Males 22; Females 50 80 mg: Males 38; Females 42 Decreased weight gain at highest dose. Decreased food utlilization at low and high doses.

		Increased thyroxine levels in males. Decreased T 3 in high dose males, decreased thyroxine levels in high dose females. Decreased heart and kidney weights in males nondose dependent. The incidence of the following lesions were comparable to the incidence occurring in historical controls: mid dose male 1/50 renal lipoma, high dose male 3/50 and female 1/50 renal liposarcoma

Table 4: Mutagenicity

Ames Test	Negative
Mouse Lymphoma Test	Negative
Chromosomal Aberration	Negative
Test Unscheduled DNA Synthesis	Negative
Micronucleus Test	Negative

Table 5: Reproduction and Teratology

Species/Route	**Dosage mg/kg/day**	**Signs of Toxicity**
Rat p.o. Reproductive Function and Fertility (Segment I)	4, 20, 100	FO: Dose dependent lethargy, slightly decreased weight gain in males at 20 and 100 mg before pairing, variable weight gain after pairing. Irregular estrous and increased pre-coital interval at high dose. Liver lesions at high dose in 2 females.. FI: non-dose dependent variations in growth during gestation and lactation in females. Reduced activity scores in males at 100 mg. Increased swimming times in females at 100 mg.
Rat p.o. Teratology (Segment II)	4, 20, 100	Mortality: 3 females died and 2 females sacrificed at high dose. Lethargy, ataxia and piloerection. Transient decreased weight gain. Decreased fetal weight at high dose. Early resorptions and post-implantation loss increased in treated and control animals. Necropsy: At 20 mg four fetuses exhibited abnormalities of soft and skeletal tissue. At high dose slightly increased change associated with: weight reduction involved brain, soft tissue arrangement and skeletal ossification, darkened adrenal medulla. Gross Visceral Observations: External Observation- Changes mostly comparable to historical control means except for small fetus size in high dose. Internal Observations - Changes comparable to historical control means or to study control. Skeletal Observations - Changes comparable to historical control means or study controls except for slight reductions in degree of ossification of cranial bones, sternebrae, and caudal vertebrae at high dose; these were considered to be associated with reduced fetal weight.

Species/Route	Dosage mg/kg/day	Signs of Toxicity
Rabbit p.o. Teratology (Segment II)	1, 4, 16	Sedation, transient decreased weight gain. Increased pre-implantation loss at low dose and post-implantation loss at high dose. Changes included 3 small fetuses at mid dose, increased absent sternebrae at high dose and increased incomplete ossification at low and mid doses.
Rat p.o. Peri and Post-natal Development (Segment III)	4, 20, 100	Dose dependent lethargy, unsteadiness and ataxia. Gasping and impairment of righting reflex at mid and high dose. Decreased weight gain and 2 mortalities in high dose. At high dose, litters exhibited much reduced pre- and post-natal survival, mean litter size during lactation and birth weight of off-spring, extensive cannibalization and maternally inflicted injury.
Rat p.o. Milk production		Zolpidem inhibited the secretion of milk. The no-effect dose was 4 mg base / kg or 6 times the recommended human dose in mg / m^2.

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PART III: CONSUMER INFORMATION

T/C **SUBLINOX®**
Zolpidem tartrate
sublingual orally disintegrating tablets (ODT)

This leaflet is part III of a three-part "Product Monograph" published when SUBLINOX was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about SUBLINOX. Contact your doctor or pharmacist if you have any questions about the drug.

WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT SUBLINOX

Serious Warnings and Precautions

Complex sleep-related behaviours
There have been reports of people getting out of bed while not fully awake after taking SUBLINOX and doing activities that they did not know they were doing. The next morning, they did not remember doing those activities. This unusual behaviour is more likely to occur when SUBLINOX is taken with alcohol or other drugs that can make you sleepy such as those for the treatment of depression or anxiety. The activities you may do in these situations can put you and people around you in danger. Reported activities included driving a car ("sleep-driving"), leaving the house, making and eating food, talking on the phone, etc.

Important:
1. Do not take more SUBLINOX than prescribed.
2. Do not take SUBLINOX if you drink alcohol.
3. Do not take SUBLINOX if you have had episodes of sleepwalking in the past, or if there is a history of sleepwalking in your family.
4. Talk to your doctor if you have a condition that affects your sleep, such as Periodic Limb Movement in Sleep (involuntary movement of limbs during sleep) or Restless Legs Syndrome (urge to move legs, usually accompanied by uncomfortable and unpleasant sensations, that begins or worsens during periods of inactivity, typically in the evening and night)
5. Talk to your doctor about all of your medicines, including over-the-counter medicines and herbal products. Your doctor will tell you if you can take SUBLINOX with your other medicines.
6. You and people close to you should watch for the type of unusual behaviour described above. If you find out that you have done *any* such activities for which you have no memory you should call your doctor immediately.

ABOUT THIS MEDICATION

What the medication is used for:
SUBLINOX is a sleep medicine (sedative-hypnotic). SUBLINOX is used in adults for the short-term treatment of a sleep problem called insomnia. The main symptom of insomnia is trouble falling asleep. SUBLINOX is not for use in children under 18 years of age.

What it does:
SUBLINOX is one of several prescription sleeping pills that have generally similar properties such as a calming effect.
If you are prescribed sleep medications, you should consider both their benefits and risks. Important risks and limitations include the following:
- you may become dependent on the medication,
- the medication may affect your mental alertness or memory, particularly when not taken as prescribed.

(see **Warnings and Precautions**)

When it should not be used:
Do not use SUBLINOX if you have:
- a muscular disease known as myasthenia gravis
- a severe hepatic insufficiency (liver problems)
- severe lung or respiratory disease, including sleep apnea
- had episodes of sleepwalking in the past, or if there is a history of sleepwalking in your family
- Do not take SUBLINOX if you are allergic to zolpidem or any of the inactive ingredients. See below "What the non-medicinal ingredients are". Some signs of allergic reaction may be swelling of the face, a feeling of the throat closing, or difficulty breathing shortly after taking SUBLINOX.

What the medicinal ingredient is:
Zolpidem tartrate

What the nonmedicinal ingredients are:
Colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, mannitol, saccharin sodium, silicified microcrystalline cellulose**.**

What dosage forms it comes in:
Rapidly disintegrating oral tablets that you put under the tongue in 5 mg and 10 mg strengths.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Complex sleep-related behaviours:
See **What is the most important information I should know about SUBLINOX**

Need to diagnose other existing conditions
Sleep problems can be a symptom of many physical and psychiatric disorders. Your doctor will need to evaluate your medical history before initiating treatment with SUBLINOX. If your sleep problems do not stop after 7 to 10 days of treatment, this is an indication that there is another original illness that need to be evaluated. Worsening of your sleep problems or the developing 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 SUBLINOX.

Severe allergic reactions
Rare cases of swelling involving the tongue, glottis, or larynx have been reported in patients after taking the first or subsequent doses of sedative -hypnotics, including zolpidem tartrate. Some patients have had additional symptoms such as shortness of breath, throat closing, or nausea and vomiting that suggest an allergic shock reaction (which is a sudden severe and potentially fatal allergic reaction in somebody sensitive to a substance, marked by a drop in blood pressure, difficulty in breathing, itching, and swelling). Some patients have required medical therapy in the emergency department. Get emergency medical help if you get these symptoms after taking SUBLINOX.

If you suffered once from the above, you should not take this drug again.

Mental Alertness
SUBLINOX may affect your ability to be alert the next day after taking it. DO NOT DRIVE A CAR or operate potentially dangerous machinery until you experience how this drug will affect you.

Memory problems
SUBLINOX may cause a special type of memory loss (amnesia); you may not recall events that occurred during some period of time, usually several hours, after taking the drug. This lapse is usually not a problem, because the person taking the sleeping pill intends to be asleep during this critical period of time. But it can be a problem if you take the medication to induce sleep while travelling, such as during an airplane flight, because you may wake up before the effect of the drug is gone. This has been called "traveller's amnesia". DO NOT TAKE SUBLINOX when a full night's sleep is not possible before you would again need to be active and functional; e.g., an overnight flight of less than 8 hours. Memory lapses may occur in such situations. Your body needs time to eliminate the medication from your system.

Tolerance/Withdrawal Symptoms
After nightly use, sleeping pills may lose some of their effectiveness and you may also develop a degree of dependence.

When taking SUBLINOX, you may get awakened during the last third of the night or feel anxious or nervous during the day. If this occurs, tell your doctor.

You may also experience "withdrawal effects" when you stop the medication after taking it for only a week or two. But usually, these withdrawal effects are more common and severe after long periods of continuous use. For instance, on the first few nights after stopping the medication, you may find that insomnia is worse than before taking the sleeping pills. This type of withdrawal symptom is known as "rebound insomnia".

Other withdrawal effects following abrupt stopping of sleeping pills may range from unpleasant feelings to a major withdrawal syndrome that may include abdominal and muscle cramps, vomiting, sweating, tremor, and rarely, convulsions. The severe symptoms are uncommon. If you have been taking sleeping pills for a long time, discuss with your physician when and how it would be best for you to stop.

Dependence/Abuse
All prescription sleeping pills can cause dependence (addiction) especially when used regularly for more than a few weeks, or at higher doses. Some people develop a need to continue taking these drugs, not only for continued therapeutic effect, but also to avoid withdrawal symptoms or to achieve non-therapeutic effects.

Individuals who depend, or have depended at any time in the past, on alcohol or other drugs may be at particular risk of becoming dependent on drugs of this class. But **all people are at some risk**. Consider this matter before you take these medications beyond a few weeks.

Mental and Behavioural Changes
A variety of abnormal thinking and behavioural changes may occur when you use prescription sleeping pills. Some of these changes include aggressiveness and extroversion which seem out of character. Other changes, although rare, can be more unusual and extreme. These include confusion, strange behaviour, restlessness, irritability, illusions, nightmares, hallucinations, feeling like you are not yourself, and feeling more depressed, which may lead to suicidal thinking.

It is rarely clear whether such symptoms are caused by the medication, or by an illness that was present before the medication was used, or are simply spontaneous happenings. If you develop any unusual disturbing thoughts or behaviour while using SUBLINOX, discuss the matter immediately with your doctor.

Worsening of Side Effects
DO NOT CONSUME ALCOHOL WHILE TAKING SUBLINOX. Some medicines may also worsen side effects that some patients experience with SUBLINOX (see **Interactions with this medication**).

Elderly (65 years of age or older)
An increased risk of falls and fractures has been reported in elderly people who take sleeping pills such as SUBLINOX. A lower dose is recommended in the elderly (see **Proper Use of this Medication**).

Effects on Pregnancy
Certain sleeping pills have been linked to birth defects when taken during the early months of pregnancy. It is not yet known if SUBLINOX could cause similar effects. In addition, sleeping pills taken during the last weeks of pregnancy have been known to sedate the baby and may also cause withdrawal symptoms after birth. Therefore, **DO NOT TAKE** SUBLINOX at anytime during pregnancy, it may affect the developing baby.

Use in Nursing Mothers
SUBLINOX passes into breast milk. Therefore, if you are breast feeding, this medicine should be avoided. Your doctor will discuss this with you.

BEFORE you use SUBLINOX talk to your doctor or pharmacist if:

- you have a lung disease or breathing problems

- you have myasthenia gravis
- any other diseases
- you suffer from depression or have a history of depression and/or suicidal thoughts
- you are taking any other medicines, including over-the-counter medicines and herbal products
- You consume alcohol.
- You have had unexpected reactions to alcohol or sedative medications in the past, such as irritability, aggression, hallucinations, etc.
- you have a history of addiction to, or abuse of drugs or alcohol
- you have a liver or kidney disease
- you are pregnant or planning to become pregnant, or if you become pregnant while taking this medication
- you are breast feeding

INTERACTIONS WITH THIS MEDICATION

Do not use SUBLINOX if you drink alcohol. **Do not use SUBLINOX** along with other medications, over-the counter medicines or herbal products without first discussing this with your doctor or pharmacist.

SUBLINOX may produce more pronounced side effects when co-administered with:

- Alcohol
- Other tranquilizers or sleeping pills
- Sedative antihistamines
- Anticonvulsants (medicines used to control or prevent convulsions)
- Narcotic analgesics
- Antipsychotics, antidepressants and other psychotropic medications (mood altering drugs) which themselves can make you sleepy.

Other drugs which may interact with SUBLINOX by affecting the way the drug is metabolized by the enzyme CYP3A4 in the liver include:

- CYP3A4 inhibitors, such as erythromycin, clarithromycin, ketoconazole, itraconazole, and ritonavir;
- CYP3A4 inducers, such as rifampicin or rifampin, carbamazepine, phenobarbital, phenytoin, and St. John's wort.

PROPER USE OF THIS MEDICATION

How should I take SUBLINOX?

- Follow your doctor's advice about how to take SUBLINOX, when to take it, and how long to take it. Do not take more SUBLINOX than prescribed for you.
- **Take SUBLINOX right before you get into bed. Do not take SUBLINOX in the middle of the night or at any time other than at bedtime.**
- **Do not take SUBLINOX unless you are able to stay in bed a full night (7-8 hours) before you must be active again.**
- For faster sleep onset, SUBLINOX should NOT be taken with or right after a meal.
- **Do not take SUBLINOX** if you drink alcohol.
- **Do not drive a car** or operate potentially dangerous machinery until you experience how this drug will affect you the next day.
- Do not use the tablet if the seal on the blister pack is broken, or if the blister holding the tablet is broken.
- To open the blister pack, separate the individual blisters at the perforations. Peel off the top layer of paper, and push the tablet through the foil.
- Place the whole tablet under the tongue, where it will disintegrate. Do not chew or swallow or take with water.
- Treatment with SUBLINOX should usually not exceed 7-10 consecutive days. **Do not take SUBLINOX** for more than 7-10 days without first consulting your doctor.
- Call your doctor 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.
- **Do not take SUBLINOX** if it is not prescribed for you.
- SUBLINOX is not indicated for patients under 18 years of age. **Do not take SUBLINOX if you are under 18 years of age.**
- If you take too much SUBLINOX or overdose, call your doctor or poison control center right away, or get emergency treatment

Usual dose:

Adults:

The recommended initial dose is 5 mg for women and either 5 or 10 mg for men, taken only once per night immediately before bedtime with at least 7-8 hours remaining before the planned time of awakening. The total SUBLINOX daily dose should not exceed 10 mg.

Elderly (65 years of age or older): The recommended SUBLINOX dosage is 5 mg in these patients.

Patients with liver disease: The recommended SUBLINOX dosage is 5 mg.

Overdose:

For management of suspected drug overdose, contact your physician or regional Poison Control Centre immediately or go to the nearest emergency room, even if you don't feel sick.

Signs of overdose can range from feeling sleepy or ready to fall asleep to losing consciousness. As well problems with the heart and breathing have been reported.

Missed Dose:

You should only take SUBLINOX when you are ready to get into bed and go to sleep, or once in bed and have not been able to fall asleep.

If you forget to take your tablet at bedtime, do not take it at any other time, otherwise you may feel drowsy, dizzy and confused during the day; do not take SUBLINOX in the middle of the night; do not take a double dose to make up for the missed dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Serious side effects of SUBLINOX include:

- **Getting out of bed while not being fully awake and do an activity that you do not know you are doing.** (See Serious Warnings and Precautions, Complex Sleep-related behaviours)
- **Abnormal thoughts and behavior** Symptoms include more outgoing or aggressive behavior than normal, confusion, agitation, hallucinations, worsening of depression, 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 SUBLINOX.

Call your doctor right away if you have any of the above side effects or any other side effects that worry you while using SUBLINOX.

The most common side effects of SUBLINOX are:

- drowsiness
- dizziness
- diarrhea
- "drugged feelings"
- fatigue
- headache

You may still feel drowsy the next day after taking SUBLINOX.

Do not drive or do any dangerous activities after taking SUBLINOX until you feel fully awake.

Elderly patients are especially susceptible to side effects. Excessive drowsiness in the elderly may result in falls and fractures. A lower dose is recommended in the elderly (see **Proper Use of this Medication**).

After you stop taking a sleep medicine, you may have symptoms for 1 to 2 days such as:
Trouble sleeping, nausea, flushing, lightheadedness, uncontrolled crying, vomiting, stomach cramps, panic attack, nervousness, and stomach area pain (see **Warnings and Precautions, Tolerance/Withdrawal Symptoms**).

These are not all the side effects of SUBLINOX. Ask your doctor or pharmacist for more information.

Call your doctor for medical advice about side effects.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist right away		Seek urgent medical attention
		Only if severe	In all cases	
Common	Drowsiness, dizziness, diarrhea, feeling "drugged", fatigue, headache	✓		
	Unexpected reactions such as excitement, agitation, hyperactivity, hallucination, worsened insomnia, aggressiveness, irritability, rages, psychoses, and violent behaviour Depressed Mood	✓	✓	
	Severe allergic reactions (swelling of the tongue or throat, trouble breathing, nausea and vomiting)			✓
	Trouble breathing		✓	
	Withdrawal effects (abdominal and muscle cramps, vomiting, sweating, tremor, and rarely, convulsions)		✓	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk with your doctor or pharmacist right away**		**Seek urgent medical attention**
Rare	Somnambulism (sleepwalking) – getting out of bed while not fully awake and do activities you do not remember the day after		✓	
Very rare	thoughts of death or suicide		✓	

This is not a complete list of side effects. For any unexpected effects while taking SUBLINOX, contact your doctor or pharmacist.

HOW TO STORE IT

Store SUBLINOX between 15º to 30ºC (59º and 86ºF).
Protect from light and moisture.
Keep SUBLINOX and all medicines out of reach of children and pets.

General information about SUBLINOX

- Medicines are sometimes prescribed for purposes other than those listed in this Consumer Information Leaflet.
- Do not use SUBLINOX for a condition for which it was not prescribed.
- Do not share SUBLINOX with 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 Consumer Information Leaflet summarizes the most important information about SUBLINOX.

If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about SUBLINOX that is written for healthcare professionals.

For more information about SUBLINOX you can also call Bausch Health, Canada Inc.at 1-800-361-4261

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/news/media-room/advisories-warnings/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full Product Monograph, prepared for health professionals can be found at:
http://webprod3.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp
or by contacting Bausch Health, Canada Inc.at:
1-800-361-4261

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