

PRODUCT MONOGRAPH

Pr SANDOZ ZOPICLONE
Zopiclone

5 mg and 7.5 mg tablets

Hypnotic and Sedative

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5.0 mg and 7.5 mg tablets

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Oral	Tablets / 5 mg and 7.5 mg	Calcium hydrogen phosphate dihydrate, cornstarch, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, maltodextrin, polydextrose, polyethylene glycol, sodium croscarmellose, titanium dioxide and triacetin. The 7.5 mg tablet also contains: D&C yellow no.10 aluminum lake, FD&C blue no.1 aluminum lake and FD&C blue no.2 aluminum lake.

INDICATIONS AND CLINICAL USE

Sleep disturbance may be the presenting manifestation of a physical and/or psychiatric disorder. Consequently, a decision to initiate symptomatic treatment of insomnia should only be made after the patient has been carefully evaluated.

Sandoz Zopiclone (zopiclone) 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 Sandoz Zopiclone should usually not exceed 7 to 10 consecutive days. Use for more than 2 to 3 consecutive weeks requires complete re-evaluation of the patient. Prescriptions for Sandoz Zopiclone should be written for short-term use (7 to 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):

Because some of the adverse effects of zopiclone may be dose related, the smallest possible effective dose should be prescribed for elderly patients. Inappropriate, heavy sedation in the elderly, may result in accidental events/falls (See DOSAGE AND ADMINISTRATION).

Pediatrics (<18 years of age):

The safety and effectiveness of zopiclone in children and young adults below the age of 18 have not been established. Therefore, zopiclone is not indicated for patients under 18 years of age.

CONTRAINDICATIONS

Sandoz Zopiclone is contraindicated in patients with:

- known hypersensitivity to the drug or to any component or its formulation. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING section.
- myasthenia gravis
- severe hepatic insufficiency
- severe impairment of respiratory function (e.g., significant sleep apnea syndrome).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Sleep disturbance may be the presenting manifestation of a physical and/or psychiatric disorder. Consequently, a decision to initiate symptomatic treatment of insomnia should only be made after the patient has been carefully evaluated.
- Sandoz Zopiclone (zopiclone) should be used with caution in patients who in the past manifested paradoxical reactions to alcohol and/or sedative medications.
- Benzodiazepines may cause fetal damage when administered during pregnancy (See WARNINGS AND PRECAUTIONS).
- Patients should be warned not to take zopiclone under circumstances in which a full night's sleep and clearance of the drug from the body are not possible before they need again to resume full activity.
- Patients requiring mental alertness / driving:
Because of zopiclone pharmacological properties and CNS depressant effect, Sandoz Zopiclone may adversely affect the ability to drive or use machines. Patients receiving the drug should be cautioned against engaging in hazardous occupations requiring complete mental alertness such as operating machinery or driving a motor vehicle. For the same reason, patients should be warned against the concomitant ingestion of zopiclone and alcohol or CNS depressant drugs (see DRUG INTERACTIONS).

General

Benzodiazepine and benzodiazepine-like compounds should be used with extreme caution in patients with a history of substance or alcohol abuse.

Because some of the adverse effects of zopiclone 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. The use of the lowest effective dose is also consistent with management of other dose-related risks associated with zopiclone (see below: Amnesia, Complex sleep-related behaviours, CNS Depressant Effects and Next-Day Impairment, Drug abuse, dependence and withdrawal).

The cause of insomnia should be identified wherever possible and the underlying factors treated before a hypnotic is prescribed. The failure of insomnia to remit after 7-10 days of treatment may indicate the presence of a primary psychiatric and/or medical illness or the presence of sleep state misperception.

Worsening of insomnia or the emergence of new abnormalities of thinking or behaviour may be the consequence of an unrecognized psychiatric or physical disorder. These have also been reported to occur in association with the use of drugs that act at the benzodiazepine receptors.

Sandoz Zopiclone should be used with caution in patients who in the past manifested paradoxical reactions to alcohol and/or sedative medications.

Lactose is a non-medicinal ingredient in Sandoz Zopiclone. Patients with rare hereditary diseases of galactose intolerance (galactosemia or glucose-galactose malabsorption) should not take Sandoz Zopiclone.

Carcinogenesis and Mutagenesis

See TOXICOLOGY section

Drug abuse, dependence and withdrawal

Use of sedative/hypnotics agents like Sandoz Zopiclone may lead to the development of physical and psychological dependence or abuse. The risk of dependence or abuse is increased with the dose and duration of treatment, if used with alcohol or other psychotropics, in patients with a history of alcoholism and/or drug abuse or in patients with marked personality disorders. Interdose daytime anxiety and rebound anxiety may increase the risk of dependency in zopiclone treated patients. Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms.

Withdrawal symptoms, similar in character to those noted with barbiturates and alcohol (convulsions, tremor, abdominal and muscle cramps, vomiting, sweating, dysphoria, perceptual disturbances and insomnia) have occurred following abrupt discontinuation of benzodiazepines

and benzodiazepine-like agents, including zopiclone. The more severe symptoms are usually associated with higher dosages and longer usage, although patients given therapeutic dosages for as few as 1-2 weeks can also have withdrawal symptoms including daytime anxiety between nightly doses.

Consequently, abrupt discontinuation should be avoided and a gradual dosage tapering schedule is recommended in any patient taking the drug for more than a few weeks. The recommendation for tapering is particularly important in patients with a history of seizures (see ADVERSE REACTIONS, Withdrawal Symptoms).

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

It may be useful to inform the patient when treatment is started that it will be of limited duration and to explain precisely how the dosage will be progressively decreased.

Tolerance

Some loss of efficacy of other hypnotics may develop after repeated use. However, there was an absence of tolerance with zopiclone for treatment periods of up to 4 weeks.

Patients with specific conditions

Sandoz Zopiclone should be given with caution to patients with impaired hepatic or renal function, or severe chronic pulmonary insufficiency. Dosage adjustments are recommended (see DOSAGE AND ADMINISTRATION). Respiratory depression has been reported in patients with compromised respiratory function. As hypnotics have the capacity to depress respiratory drive, precautions should be observed if Sandoz Zopiclone is prescribed to patients with compromised respiratory function.

Zopiclone is contraindicated in patients with myasthenia gravis and severe hepatic insufficiency and in those with severe impairment of respiratory function, e.g., significant sleep apnea syndrome (see CONTRAINDICATIONS).

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 zopiclone. 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 Sandoz Zopiclone should not be rechallenged with the drug.

Neurologic

Patients requiring mental alertness

Because of zopiclone's pharmacological properties and CNS depressant effect, zopiclone may adversely affect the ability to drive or use machines. Patients receiving the drug should be cautioned against engaging in hazardous occupations requiring complete mental alertness such as operating machinery or driving a motor vehicle. For the same reason, patients should be warned against the concomitant ingestion of zopiclone and alcohol or CNS depressant drugs (see DRUG INTERACTIONS).

CNS Depressant Effects and Next-Day Impairment

Like other sedative/hypnotic drugs, Sandoz Zopiclone has CNS-depressant effects. Due to the rapid onset of action, Sandoz Zopiclone 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 Sandoz Zopiclone. The risk of next day psychomotor impairment, including impaired driving, is increased if zopiclone is taken with less than a full night of sleep remaining; 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 zopiclone.

Patients should be cautioned against taking Sandoz Zopiclone in these circumstances.

The lowest effective dose for the patient should be used.

Zopiclone is not to be taken with alcohol or other sedative hypnotics (including other zopiclone products) at bedtime or the middle of the night. If concomitant use of another CNS depressant or a drug that increases zopiclone blood levels is clinically warranted, dosage adjustments of zopiclone may be necessary.

Even if zopiclone is taken as instructed, some patients may still have zopiclone blood levels in the morning high enough to produce impairment (see DOSAGE AND ADMINISTRATION and DRUG INTERACTIONS).

Patient counseling information regarding next-day impairment: Tell patients that Sandoz Zopiclone 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 Sandoz Zopiclone as instructed and do not feel drowsy in the morning, they still have to wait for at least 12 hours after dosing before driving or engaging in other activities requiring full mental alertness, especially for elderly patients and for patients who take the 7.5 mg dose. Inform patients that impairment can be present despite feeling fully awake.

Amnesia

Anterograde amnesia of varying severity has been reported following therapeutic doses of benzodiazepines or benzodiazepine-like agents. The event is rare with zopiclone. Anterograde amnesia may occur, especially when sleep is interrupted or when retiring to bed is delayed after the intake of the tablet. 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 travelling. Transient global amnesia and traveller's amnesia are unpredictable and not necessarily dose-related phenomena. To reduce the possibility of anterograde amnesia, patients should ensure that they take the tablet strictly when retiring for the night. Patients should be warned not to take Sandoz Zopiclone under circumstances in which a full night's sleep and clearance of the drug from the body are not possible before they need again to resume full activity.

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 zopiclone. 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 zopiclone alone at therapeutic doses, the use of alcohol and other CNS-depressants with zopiclone appears to increase the risk of such behaviours, as does the use of zopiclone at doses exceeding the maximum recommended dose.

Sandoz Zopiclone is not to be taken with alcohol.

Caution is needed with concomitant use of other CNS depressants drugs.

Caution is recommended in patients with a personal or family history of sleepwalking. Although complex sleep-related 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 Sandoz Zopiclone.

The use of Sandoz Zopiclone 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.

Treatment with Sandoz Zopiclone 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 Sandoz Zopiclone should be strongly considered for patients who report any such complex sleep-related behaviours.

Rebound insomnia

A transient syndrome whereby the symptoms that led to treatment with a benzodiazepine or benzodiazepine-like agent 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.

Since the risk of such phenomena is greater after abrupt discontinuation of zopiclone, especially after prolonged treatment, it is, therefore recommended to decrease the dosage gradually and to advise the patient accordingly (see ADVERSE REACTIONS). It is important that the patient should be aware of the possibility of rebound phenomena, thereby minimizing anxiety over such symptoms should they occur while the medicinal product is being discontinued.

Psychiatric

Abnormal thinking and psychotic behavioural changes

Abnormal thinking and other behavioural changes have been reported to occur in association with the use of benzodiazepines and benzodiazepine-like agents including zopiclone, although rarely (see ADVERSE REACTIONS). Some of the changes may be characterized by decreased inhibition, e.g., aggression or extroversion that seems excessive, similar to that seen with alcohol and other CNS depressants (e.g., sedative/hypnotics). Particular caution is warranted in patients with a history of violent behaviour and a history of unusual reactions to sedatives including alcohol and the benzodiazepines or benzodiazepine-like agents. Psychotic behavioural changes that have been reported include abnormal behaviour, restlessness, agitation, irritability, hallucinations, delusion, anger, nightmare and depersonalization. Abnormal behaviours 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.

It can rarely be determined with certainty whether a particular instance of abnormal behaviours listed above is drug induced, spontaneous in origin, or a result of an underlying psychiatric disorder. Nevertheless, the emergence of any new behavioural 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

The benzodiazepines and benzodiazepine-like agents affect mental efficiency, e.g., concentration, attention and vigilance. The risk of confusion is greater in the elderly and in patients with cerebral impairment.

Anxiety, restlessness

An increase in daytime anxiety and/or restlessness have been observed during treatment with zopiclone. This may be a manifestation of interdose withdrawal, due to the short elimination half-life of the drug.

Depression

Caution should be exercised if Sandoz Zopiclone is prescribed to patients with signs and symptoms of depression that could be intensified by hypnotic drugs. The potential for self-harm (e.g., intentional overdose) is high in patients with depression and thus, the least amount of drug that is feasible should be available to them at any one time.

As with other hypnotics, zopiclone does not constitute a treatment of depression and may even mask its symptoms.

Renal

Zopiclone should be given with caution to patients with impaired renal function. Dosage adjustments are recommended (see DOSAGE AND ADMINISTRATION).

Skin

Rashes may be a sign of drug hypersensitivity. Zopiclone use should be discontinued if this occurs (see ADVERSE REACTIONS).

Special Populations

Pregnant Women: The use of zopiclone during pregnancy is not recommended.

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.

Insufficient data are available on zopiclone to assess its safety during human pregnancy. Thus, the use of Sandoz Zopiclone during pregnancy is not recommended. If Sandoz Zopiclone 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.

During the last weeks of pregnancy, ingestion of therapeutic doses of benzodiazepine hypnotic drugs has resulted in neonatal CNS depression due to transplacental distribution. Similar effects can be expected to occur with zopiclone, due to its pharmacological effects. If Sandoz Zopiclone is used during the last three months of pregnancy or during labour, effects on the neonate, such as hypothermia, hypotonia, and respiratory depression can be expected.

A child born to a mother who took sedative/hypnotics agents chronically during the latter stages of pregnancy may have developed physical dependence and may be at risk for developing withdrawal symptoms in the postnatal period.

Nursing Women: Zopiclone is excreted in human milk, and its concentration may reach 50% of the plasma levels. Insufficient data are available on zopiclone to assess its safety during lactation. Therefore, the administration of Sandoz Zopiclone to nursing mothers is not recommended.

Pediatrics (< 18 years of age):

The safety and effectiveness of zopiclone in children and young adults below the age of 18 have not been established. Sandoz Zopiclone should not be prescribed in pediatric patients.

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. Therefore, the Sandoz Zopiclone dose in elderly patients should not exceed 5 mg (see DOSAGE AND ADMINISTRATION, Geriatric patients). Anterograde amnesia is a dose-related phenomenon and elderly subjects may be at particular risk.

Monitoring and Laboratory Tests

There have been sporadic reports of abnormal laboratory test values including increase in AST, ALT or alkaline phosphatase values.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most common adverse reaction seen with zopiclone is taste alteration (bitter taste). Severe drowsiness and/or impaired coordination are signs of drug intolerance or excessive doses.

Clinical Trial Adverse Drug Reactions

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.

The following adverse events were observed in patients receiving zopiclone. In the absence of an established cause-effect relationship those adverse reactions that were observed more frequently with zopiclone than with a placebo are in italic.

Central nervous system: *Somnolence, dizziness, confusion, anterograde amnesia or memory impairment, feeling of drunkenness, euphoria, nightmares, agitation, anxiety or nervousness, hostility, depression, decreased libido, libido disorder, coordination abnormality, headache, hypotonia, tremor, muscle spasms, paresthesia, and speech disorder.*

Hallucinations, aggression, irritability and fall (predominantly in elderly patients).

Cardiovascular: Palpitations

Digestive: *Bitter taste, dry mouth, coated tongue, bad breath, nausea, vomiting, dyspepsia, diarrhea, constipation, anorexia or increased appetite.*

General Disorders and Administration Site Conditions: *asthenia, chills, fatigue*

Respiratory: Dyspnea

Special senses: Amblyopia

Dermatologic: Rash, spots on skin, sweating, pruritus. Rashes and pruritus may be a sign of drug hypersensitivity; discontinue if this occurs.

Angioedema and/or anaphylactic reactions have been reported very rarely.

Metabolic and nutritional: Weight loss

Musculoskeletal: limb heaviness

Laboratory Tests: There have been sporadic reports of abnormal laboratory test values. Mild to moderate increases in serum transaminase and/or blood alkaline phosphatase have been reported very rarely.

Geriatric patients: Geriatric patients tended to have a higher incidence of palpitations, vomiting, anorexia, sialorrhea, confusion, agitation, anxiety, tremor and sweating than younger patients. Anterograde amnesia is a dose-related phenomenon and elderly subjects may be at particular risk.

Withdrawal symptoms: Withdrawal syndrome has been reported upon discontinuation of zopiclone (see WARNINGS AND PRECAUTIONS, Drug abuse, dependence and withdrawal). Withdrawal symptoms vary and may include rebound insomnia, muscle pain, anxiety, tremor, sweating, agitation, confusion, headache, palpitations, tachycardia, delirium, nightmares, hallucinations, and irritability. In severe cases the following symptoms may occur: derealisation, depersonalisation, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations. In very rare cases, seizures may occur.

Postmarket Experience

Psychiatric disorders: restlessness, delusion, anger, abnormal behaviours (possibly associated with amnesia) and somnambulism (see WARNINGS, Complex sleep-related behaviours), withdrawal syndrome and dependence have been reported rarely.

Respiratory: respiratory depression

Nervous system disorder: ataxia, paresthesia (not associated with withdrawal)

Eye disorder: diplopia

Gastrointestinal disorders: dyspepsia

Musculoskeletal and connective tissue disorders: muscular weakness.

DRUG INTERACTIONS

Serious Drug Interactions

Zopiclone may produce additive CNS depressant effects when co-administered with sedative antihistamines, anticonvulsants, narcotic analgesics, anesthetics, or psychotropic medications which themselves can produce CNS depression.

The emergence of any new behavioral signs or symptoms require careful and immediate evaluation.

Overview

The risk of drug interaction arising from displacement of bound drug is low.

Drug-Drug Interactions

Alcohol

Concomitant intake with alcohol is not recommended (see WARNINGS, Complex sleep-related behaviours). Sandoz Zopiclone may produce additive CNS depressant effects when co-administered with alcohol.

CNS Depressants

Sandoz Zopiclone may produce additive CNS depressant effects when co-administered with sedative antihistamines, anticonvulsants, narcotic analgesics, anesthetics, or psychotropic medications such as antipsychotics (neuroleptics), hypnotics, anxiolytics/sedatives, and antidepressant agents which themselves can produce CNS depression. In the case of narcotic analgesics, enhancement of euphoria may also occur leading to an increase in psychological dependence.

Drugs Affecting Cytochrome P450 Enzymes

Since Sandoz Zopiclone is metabolized by the cytochrome P450 (CYP) 3A4 isoenzyme (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Metabolism), plasma levels of zopiclone may be increased when co-administered with CYP3A4 inhibitors, such as erythromycin, clarithromycin, ketoconazole, itraconazole, and ritonavir. A dose reduction for Sandoz Zopiclone may be required when it is co-administered with CYP3A4 inhibitors. Conversely, plasma levels of Sandoz Zopiclone may be decreased when co-administered with CYP3A4 inducers, such as rifampicin or rifampin, carbamazepine, phenobarbital, phenytoin, and St. John's wort. A dose increase for zopiclone may be required when it is co-administered with CYP3A4 inducers.

The effect of erythromycin on the pharmacokinetics of zopiclone has been studied in 10 healthy subjects. The AUC of zopiclone is increased by 80% in presence of erythromycin. The hypnotic effect of zopiclone may be enhanced when administered with erythromycin.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Lifestyle Interactions

Concomitant intake with alcohol is not recommended (see WARNINGS, Complex sleep-related behaviours). Zopiclone may produce additive CNS depressant effects when co-administered with alcohol.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

Use the lowest effective dose of Sandoz Zopiclone for the patient.

Treatment with Sandoz Zopiclone (zopiclone) should usually not exceed 7 to 10 consecutive days. Use for more than 2 to 3 consecutive weeks requires complete re-evaluation of the patient.

The product should be taken just before retiring for the night.

Adult dose

The recommended initial dose is 3.75 mg (one-half of a 7.5 mg tablet). The dose can be increased to 5 mg and further to 7.5 mg if clinically indicated. In some patients, the higher doses result in zopiclone blood levels in the morning high enough to produce impairment of driving and other activities that require full alertness (see WARNINGS, CNS Depressant Effects and Next-Day Impairment).

The 7.5 mg dose should not be exceeded (see WARNINGS AND PRECAUTIONS).

Geriatrics (\geq 65 years of age)

In the elderly and/or debilitated patient an initial dose of 3.75 mg (one-half of a 7.5 mg tablet) at bedtime is recommended. The dose may be increased to 5.0 mg if the starting dose does not offer adequate therapeutic effect.

Patients with impaired liver function : The recommended dose is 3.75 mg (one-half of 7.5 mg tablet) depending on acceptability and efficacy. Up to 7.5 mg may be used with caution in appropriate cases.

Sandoz Zopiclone (zopiclone) is contraindicated in patients with severe hepatic insufficiency (see CONTRAINDICATIONS).

Patients with renal insufficiency: Although no accumulation of zopiclone or of its metabolites has been detected in cases of renal insufficiency, it is recommended that patients with impaired renal function should start treatment with 3.75 mg (one-half of a 7.5 mg tablet). If clinically indicated, a 5 mg may be used with caution in appropriate cases.

Patients with chronic respiratory insufficiency: The recommended dose is 3.75 mg (one-half of a 7.5 mg tablet) depending on acceptability and efficacy. Up to 7.5 mg may be used with caution in appropriate cases.

Zopiclone is contraindicated in patients with severe impairment of respiratory function, e.g., significant sleep apnea syndrome (see CONTRAINDICATIONS).

Use with potent CYP3A4 inhibitors: An initial dose of 3.75 mg (one-half of a 7.5 mg tablet) at bedtime is recommended (see DRUG INTERACTIONS). If clinically indicated, a 5 mg may be used with caution in appropriate cases.

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

Pediatrics ($<$ 18 years of age)

Sandoz Zopiclone (zopiclone) is not indicated for patients under 18 years of age.

OVERDOSAGE

Signs and Symptoms

Overdose is usually manifested by varying degrees of central nervous system depression ranging from drowsiness to coma according to the quantity ingested. In mild cases, symptoms include drowsiness, confusion, and lethargy; in more severe cases, symptoms may include ataxia,

hypotonia, hypotension, methaemoglobinaemia, respiratory depression, and coma. Overdose should not be life threatening unless combined with other CNS depressants, including alcohol. Other risk factors, such as the presence of concomitant illness and the debilitated state of the patient, may contribute to the severity of symptoms and very rarely can result in fatal outcome.

In voluntary or accidental cases of zopiclone overdosage involving doses up to 340 mg, the principal effects reported were prolonged sleep, drowsiness, lethargy and ataxia.

Recommended Treatment

Symptomatic and supportive treatment in adequate clinical environment is recommended, attention should be paid to respiratory and cardiovascular functions. Gastric lavage or activated charcoal is only useful when performed soon after ingestion.

Hemodialysis is of no value due to the large volume of distribution of zopiclone. Flumazenil may be a useful antidote; however, flumazenil administration may contribute to the appearance of neurological symptoms (agitation, anxiety, convulsions and emotional lability). Intravenous fluids should be administered as needed.

Poison Control Center

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

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Zopiclone, a cyclopyrrolone derivative, is a short-acting hypnotic agent. Zopiclone is structurally unrelated to existing hypnotics. However, the pharmacological profile of zopiclone is similar to that of the benzodiazepines.

Zopiclone pharmacological properties are: hypnotic, sedative, anxiolytic, anti-convulsant, muscle-relaxant. These effects are related to a specific agonist action at central receptors belonging to the GABA_A macromolecular complex, modulating the opening of the chloride ion channel.

Pharmacodynamics

In sleep laboratory studies of one to 21-day duration in man, zopiclone reduced sleep latency, increased the duration of sleep and decreased the number of nocturnal awakenings. Zopiclone delayed the onset of REM sleep but did not reduce consistently the total duration of REM periods. The duration of stage 1 sleep was shortened, and the time spent in stage 2 sleep increased. In most studies, stage 3 and 4 sleep tended to be increased, but no change and actual

decreases have also been observed. The effect of zopiclone on stage 3 and 4 sleep differs from that of the benzodiazepines which suppress slow wave sleep. The clinical significance of this finding is not known.

With hypnotic drugs, the duration of hypnotic effect and the profile of unwanted effects may be influenced by the alpha (distribution) ($t_{1/2\alpha}$) and beta (elimination) ($t_{1/2\beta}$) half-lives of the administered drug and any active metabolites formed. When half-lives are long, the drug or metabolite may accumulate during periods of nightly administration and be associated with impairments of cognitive and motor performance during waking hours.

If half-lives are short, the drug and metabolites will be cleared before the next dose is ingested, and carry-over effects related to sedation or CNS depression should be minimal or absent. If the drug has a very short elimination half-life, it is possible that a relative deficiency (i.e., in relation to the receptor site) may occur at some point in the interval between each night's use. This sequence of events may account for two clinical findings reported to occur after several weeks of nightly use of rapidly eliminated benzodiazepines or benzodiazepine-like hypnotics: 1) increased wakefulness during the last third of the night and 2) the appearance of increased day-time anxiety (see WARNINGS AND PRECAUTIONS).

During nightly use and for an extended period, pharmacodynamic tolerance or adaptation to some effects of benzodiazepines or benzodiazepine-like hypnotics may develop. However in two sleep laboratory studies involving 17 patients, there was an absence of tolerance with zopiclone for treatment periods of more than 4 weeks.

Rebound insomnia:

Some manifestations of rebound insomnia have been reported both in sleep laboratory and clinical studies following the withdrawal of zopiclone (see WARNINGS AND PRECAUTIONS).

Zopiclone treatment was associated with dose-related residual effects (see WARNINGS AND PRECAUTIONS).

Pharmacokinetics

Absorption: Zopiclone is rapidly and well absorbed. Bioavailability is more than 75%, indicating the absence of a significant first-pass effect. After the administration of 3.75 and 7.5 mg doses, peak plasma concentrations of 30 and 60 ng/mL, respectively were reached in less than 2 hours. Absorption was similar in males and females.

Repeated daily administration of a 7.5 mg oral dose for 14 days did not change the pharmacokinetic characteristics of zopiclone and did not lead to accumulation.

Distribution: Zopiclone is rapidly distributed from the vascular compartment (distribution half-life [$t_{1/2\alpha}$]: 1.2 hours) while the elimination half-life is approximately 5 hours (range: 3.8 to 6.5 hours). Plasma protein binding is low (approximately 45% in the 25-100 ng/mL

concentration range) and non saturable. The risk of drug interaction arising from displacement of bound drug is low. The distribution volume is 91.8-104.6 liters.

Metabolism: Zopiclone is extensively metabolized by three major pathways; only about 4 to 5% of the drug is excreted unchanged in the urine.

An *in vitro* study indicates that cytochrome P450 (CYP) 3A4 is the major isoenzyme involved in the metabolism of zopiclone to both metabolites, and that CYP2C8 is also involved with N-desmethyl zopiclone formation.

The principal metabolites are the N-oxide derivative (~12%), which has weak pharmacological activity in animals, and the N-desmethyl metabolite (~16%), which is pharmacologically inactive.

Their apparent half-lives evaluated from the urinary data are approximately 4.5 and 7.4 hours, respectively. Both metabolites are excreted renally.

Other metabolites resulting from oxidative decarboxylation are partly eliminated *via* the lung as carbon dioxide. In animals, zopiclone did not induce hepatic microsomal enzymes.

Excretion: Excretion studies, using C¹⁴-zopiclone have shown that more than 90% of the administered dose was excreted over a period of 5 days, 75% being eliminated in the urine and 16% in the feces.

The low renal clearance of unchanged zopiclone (mean 8.4 mL/min) compared with that of plasma (232 mL/min) indicates that zopiclone clearance is mainly metabolic.

Special Populations and Conditions

Elderly subjects: The absolute bioavailability of zopiclone was increased (94% *vs* 77% in young subjects) and the elimination half-life prolonged (~7 hours). Accumulation has not been observed on repeated dosing.

Patients with hepatic insufficiency: Elimination half-life was substantially prolonged (11.9 hours) and time to peak plasma levels delayed (3.5 hours). Consequently, lower doses are recommended (see DOSAGE AND ADMINISTRATION).

In cirrhotic patients, the plasma clearance of zopiclone is reduced by approximately 40% in relation with the decrease of the demethylation process. Therefore, dosage will have to be modified in these patients.

Patients with mild to moderate renal insufficiency: The pharmacokinetics of zopiclone were not affected. In renal insufficiency, no accumulation of zopiclone or of its metabolites has been detected after prolonged administration.

Zopiclone is removed by hemodialysis; however, hemodialysis is of no value in treating overdose due to the large volume of distribution of zopiclone (see also OVERDOSAGE). Hemodialysis did not appear to increase the plasma clearance of the drug.

Lactating women: Zopiclone was present in the milk, its concentration paralleled plasma levels but was about 50% lower (see WARNINGS AND PRECAUTIONS, Nursing Women).

Pediatrics: No data are available.

STORAGE AND STABILITY

Store in a dry place, at room temperature (15°-30°C). Protect from light.

Keep in a safe place out of reach of children

DOSAGE FORMS, COMPOSITION AND PACKAGING

Sandoz Zopiclone (zopiclone) 5.0 mg tablets: Each white, round, biconvex, film-coated tablet debossed "RXP" on one side and with "5" on the other, contains: zopiclone 5.0 mg and are available in bottles of 100 tablets.

Sandoz Zopiclone(zopiclone) 7.5 mg tablets: Each oval, film-coated blue tablet, marked with "RXP 7.5" on one side and with a scored line on the other, contains: zopiclone 7.5 mg and are available in bottles of 100 and 500 tablets.

Composition:

Sandoz Zopiclone (zopiclone) 5.0 mg tablets contains: zopiclone 5.0 mg. **Nonmedicinal ingredients in alphabetical order:** calcium hydrogen phosphate dihydrate, cornstarch, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, maltodextrin, polydextrose, polyethylene glycol, sodium croscarmellose, titanium dioxide and triacetin.

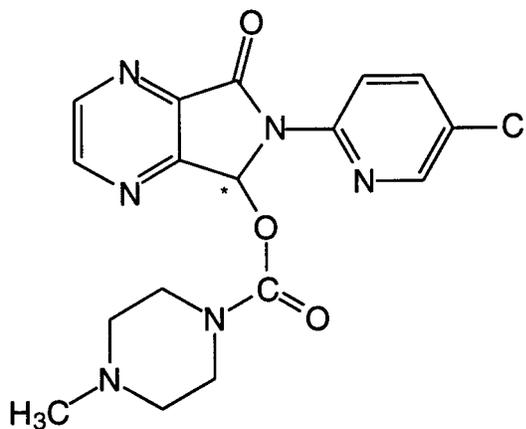
Sandoz Zopiclone (zopiclone) 7.5 mg tablet contains: zopiclone 7.5 mg. **Nonmedicinal ingredients in alphabetical order:** calcium phosphate dihydrate, cornstarch, D&C yellow no.10 aluminum lake, FD&C blue no.1 aluminum lake, FD&C blue no.2 aluminum lake, hydroxypropyl methylcellulose, lactose, magnesium stearate, maltodextrin, polydextrose, polyethylene glycol, sodium croscarmellose, titanium dioxide and triacetin.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Zopiclone
Chemical name:	(5 <i>RS</i>)-6-(5-chloropyridin-2-yl)-7-oxo-6,7-dihydro-5 <i>H</i> -pyrrolo[3,4- <i>b</i>]pyrazin-5-yl 4-methylpiperazine-1-carboxylate
Molecular formula and molecular mass:	C ₁₇ H ₁₇ ClN ₆ O ₃ and 388.82 g/mol
Structural formula:	



Physiochemical properties:	White or slightly yellowish odourless, nonhygroscopic powder.
pKa:	6.70
pH:	7.94 in a 0.05% aqueous solution.
Solubility:	Practically insoluble in water, ethanol and ethyl ether; freely soluble in methylene chloride and chloroform; and sparingly soluble in acetone and practically insoluble in alcohol. It dissolves in dilute mineral acids.
Melting point:	178°C

CLINICAL TRIALS

Comparative Bioavailability Studies

In a recently conducted study, the bioavailability of Sandoz Zopiclone (zopiclone) 7.5 mg tablets (Sandoz Canada Inc.), was compared with respect to the Canadian Reference Product, Imovane, 7.5 mg tablets (sanofi-aventis) under single dose, fasting conditions.

Of the 24 healthy adult male volunteers enrolled in this study, one did not complete the crossover. Pharmacokinetic and statistical analyses were conducted on data from 23 subjects. The relative bioavailability of Sandoz Zopiclone (manufactured by Sandoz Canada Inc.) and Imovane (manufactured by sanofi-aventis) 7.5 mg zopiclone tablets is shown in Table 1.

Table 1: Summary table of the comparative bioavailability data of Sandoz Canada Inc. (Sandoz Zopiclone) and Sanofi-Aventis (Imovane) zopiclone 7.5 mg tablets under single-dose fasting conditions.

Zopiclone (7.5 mg) From measured data Geometric Mean Arithmetic Mean (CV %)
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Parameter	Sandoz Zopiclone	Reference [†] Imovane ⁷	% Ratio of Geometric Means	90% Confidence Interval
AUC _T (ng.h/mL)	410.99 425.5 (28.9)	382.79 396.6 (28.2)	107.5*	(102.0-113.3)
AUC _I (ng.h/mL)	431.61 447.5 (29.7)	402.16 417.9 (29.3)	107.5*	(101.8-113.5)
C _{MAX} (ng/mL)	65.23 70.12 (42.6)	62.16 65.30 (36.4)	104.9*	(95.2-115.7)
T _{MAX} * (h)	1.471 (89.5)	1.417 (73.4)		
T _½ ** (h)	5.637 (11.3)	5.675 (12.8)		

* Sandoz Zopiclone is manufactured by Sandoz Canada Inc.

† Imovane ® is manufactured by sanofi-aventis Canada Inc.

* Results after correction for measured content show similar trends.

** The T_{MAX} and T_½ parameters are expressed as the arithmetic means (CV %).

Conclusion:

The 90% confidence intervals for the ln-transformed parameters AUC_T and C_{max} for zopiclone are within the 80-125% TPD acceptance range both before and after correction for measured content. Based on these results, the Sandoz Canada Inc. (Sandoz Zopiclone) and sanofi-aventis (Imovane), 7.5 mg zopiclone tablets are bioequivalent under single dose, fasting conditions.

DETAILED PHARMACOLOGY

Zopiclone, a cyclopyrrolone derivative, is a chemically novel hypnotic agent. However, the pharmacological and behavioural evaluation of the drug has shown that its effects are similar to those of the benzodiazepines.

1. CNS activity

Zopiclone antagonizes chemically and electroshock-induced seizures in mice and rats. While it potently affects convulsive conditions that involve GABA, it is relatively ineffective when glycine, another inhibitory amino acid, is involved.

Zopiclone exerts muscle relaxant activity; it inhibits the traction grasping reflex in mice, reduces the ability of mice and rats to remain on a rotarod and inclined screen, respectively, relaxes the hind legs of normal cats and blocks polysynaptic reflexes in chloralosed cats.

Zopiclone also exerts anti-aggressive activity; it inhibits footshock-induced fighting behaviour in mice and septal lesion-induced aggression in rats.

In a "conflict" situation, the drug increases punishment-suppressed lever-pressing behaviour, which is indicative of anxiolytic activity. Non-punished responding, indicative of non-specific sedation, is suppressed only at higher doses.

While zopiclone does not cause loss of righting reflex in normal mice, it potentiates narcosis induced by hexobarbital or ethanol.

In a drug discrimination paradigm, where rats are trained to discriminate drug from saline, the zopiclone discriminative stimulus generalized to several benzodiazepines as well as to pentobarbital. The finding that the benzodiazepines and a barbiturate were able to substitute for zopiclone indicates that zopiclone belongs to the same class of drugs.

Tolerance does not develop to the behavioural effects of zopiclone, since the anticonvulsant and taming ED₅₀'s are similar in naive and zopiclone-treated animals.

2. Receptor binding studies

Zopiclone has a high and specific affinity for benzodiazepine binding sites in several rat brain regions. The drug can inhibit the binding of ³H-benzodiazepines, but can itself label the sites that are recognized both by benzodiazepine agonists and Ro 15-1788, a benzodiazepine antagonist. Zopiclone does not recognize the peripheral benzodiazepine receptor sites and lacks affinity for the serotonin, GABA, α_1 and α_2 adrenergic, and dopamine receptors.

The interaction of zopiclone with the benzodiazepine receptor/GABA receptor/chloride channel complex differs somewhat from that of the benzodiazepines; while it decreases cGMP concentration in rat cerebellum, its binding is not enhanced either by GABA or by the chloride anion.

3. Dependence liability

In barbital-dependent rhesus monkeys, zopiclone suppressed the abstinence symptoms which appeared upon withdrawal. Partial and complete suppression was observed at 4 and 16 mg/kg doses, respectively.

Zopiclone, when administered to monkeys at a dose of 16 mg/kg/day for 28 days, precipitated withdrawal signs of moderate severity. Peak symptoms appeared three and four days after withdrawal and included hyperirritability, restlessness, tremor, and some weight loss. The administration of a higher dose for two weeks brought about similar symptoms upon withdrawal without precipitating convulsions.

Zopiclone was self-administered both intravenously and intragastrically in monkeys. When the drug was changed to saline, the rate of self-administration declined rapidly.

4. Cardiovascular and Respiratory Effects

Zopiclone was evaluated in conscious and anesthetized cats, dogs, rabbits and monkeys with regard to its effect on respiration and several cardiovascular parameters. Most of the studies involved IV administration.

In general, respiration and blood pressure decreased in a dose-dependent fashion while heart rate and EKG showed little change. Zopiclone affected central respiratory control mechanisms to a greater extent than the cardiovascular regulatory mechanisms.

5. Drug Interaction Studies

Zopiclone was evaluated in combination with several drugs and in general interacted either in an additive or synergistic fashion with diazepam, phenobarbital, trimethadione, chlorpromazine, hexobarbital, and ethanol. Zopiclone did not modify the effects of phenytoin, morphine, ketoprofen and gallamine.

The effects of zopiclone could be reversed by Ro 15-1788 (flumazenil) a specific benzodiazepine antagonist.

TOXICOLOGY

Acute Toxicity

Studies were carried out in both sexes of several species. The results are summarized in the following Table.

Species	Route	LD ₅₀ (mg/kg)
Mice	IV	450
	IP	580
	PO	1150
Rats	PO	2300
Dogs	PO	≥ 4500
	IV	~ 400
Cats	PO	> 1500
Rabbits	PO	~ 2500
Monkeys	PO	> 4500

Symptoms of toxicity included sedation, CNS depression, ataxia, respiratory depression, and dyspnea. In dogs, the IV administration of zopiclone was followed by myoclonic seizures.

Long-Term Toxicity Studies

1. Rats (CD strain):

One-month oral study

Ten rats/sex/dose received zopiclone by gavage six days per week at doses of 0, 6, 24 and 120 mg/kg. Dose-related sedation and paresis of hind legs were observed.

Thyroid weights were increased in male rats at all dose levels. In the high dose males, heart and spleen weights were reduced.

Three-month oral study

Fifteen rats/sex/dose received zopiclone by gavage seven days per week at doses of 0, 2, 12 and 120 mg/kg. At the mid and high doses, dose-related hypotonia, adynamia and ptosis were observed, all of which subsided with time. Weight gain was slightly but significantly less in mid and high dose male rats than in controls.

At the 120 mg/kg dose the following changes occurred. BSP values decreased in both sexes; the number of RBC decreased in females; liver weights increased in both males and females, accompanied by slight changes in the parenchymal liver cells, namely eosinophilia or basophilia in the portal area.

18-month oral study

Fifty rats/sex/dose received zopiclone in the diet at doses of 0, 2, 20 and 200 mg/kg. Of these animals 15 rats/sex/dose were sacrificed at six months. The lowest dose was well tolerated.

At the high dose the following changes were seen: weight gain was reduced by about 30% in both sexes; plasma protein levels were elevated at 3 and 6 months in the males and throughout the study in the females; albumin and globulin levels were elevated; thyroid weights were increased in male rats, accompanied by thyroid hyperplasia and, in some rats, by follicular adenomas; liver weights were increased in female rats both at 6 and 18 months; hepatocellular hypertrophy occurred in both sexes.

2. Dogs (beagle):

One-month oral study

One dog/sex/dose received zopiclone six days per week at doses of 0, 6, 24 and 120 mg/kg. Dose-related sedation and hypotonia of the hind legs were observed. High dose dogs and the intermediate dose female dog exhibited moderate weight loss.

At the high dose, both dogs had Heinz bodies in circulating erythrocytes and the bone marrow showed erythroblastic hyperplasia. In addition, the male animal had marked anemia and active erythropoiesis in the spleen. BUN values were increased at all doses in a dose-related fashion; liver function tests were somewhat elevated.

Six-month oral study

Six dogs/sex/dose received zopiclone seven days per week at doses of 0, 5, 10 and 25 mg/kg. One dog/sex from each group was sacrificed after a 3-month recovery period. Zopiclone caused slight excitation, ataxia and drowsiness, and drowsiness and sleep at the 5, 10, and 25 mg/kg doses respectively. Late in the study, four dogs had epileptoid seizures and three of them died. A reduced weight gain was observed only in high dose male dogs.

Platelet counts rose substantially above normal in two high dose female dogs. Transaminase levels were elevated but not in a dose-dependant manner. Alkaline phosphatase levels were significantly elevated both in male and female dogs, receiving the 25 mg/kg dose.

While liver weights increased both in male and female dogs in a dose-dependent fashion, they returned toward control values following the 3-month recovery period. In high dose male animals, relative spleen, kidney and adrenal weights were significantly increased. Examination of bone marrow smears showed that the proportion of proerythroblasts and the ratio of normoblasts to basophilic erythroblasts were significantly greater in high dose females than in controls.

One-year oral study

Five dogs/sex/dose received zopiclone seven days per week at doses of 0, 1, 5 and 25 mg/kg. Zopiclone induced ataxia, sleepiness, lethargy, decreased activity, body tremors and excitability. The latter two effects occurred prior to dosing, while the others were seen shortly after dosing. After six months of treatment, zopiclone induced epileptoid seizures in five dogs (four high dose, one mid dose). Since the convulsions were observed early morning prior to dosing, they might have been a manifestation of withdrawal. Female dogs, treated with 5 mg/kg of zopiclone, were significantly heavier than controls. Treated animals both ate and drank more than did their respective controls.

Platelet counts were elevated in both sexes at the 5 and 25 mg/kg doses. Alkaline phosphatase was elevated from the first month on in mid and high dose animals. T₄ values in high dose males and BSP values in high dose females were also elevated.

There was a dose-dependent increase in liver weights which became statistically significant at the 25 mg/kg dose. The elevated liver weights were associated with histopathological changes, namely vacuolation of hepatocyte cytoplasm with eosinophilic hyaline bodies.

Carcinogenicity

Oncogenicity studies were carried out with zopiclone in rats and mice with doses of 1, 10 and 100 mg/kg/day for two years. There was an increased incidence of mammary tumours with a shift toward more anaplastic forms in female and an increase of thyroid tumours in male rats on the high dose. In the mouse study, females on the high dose had an increased incidence of pulmonary adenocarcinomas; while males on the high dose had a high number of subcutaneous soft tissue tumours.

In a wide battery of tests, it was shown that zopiclone has no mutagenic or clastogenic (chromosome-damaging) properties; urine extracts from zopiclone treated mice, rats and humans were similarly not mutagenic.

The effect of zopiclone is that of a non-genotoxic oncogen; tumor redistribution phenomena are frequently observed in rodent carcinogenicity studies, particularly with drugs acting on the central nervous system and the hormonal balance. The rise of 17 beta-estradiol may be regarded as a cause for the emergence of mammary tumours and the shift from well differentiated to poorly differentiated mammary carcinomas. The altered feedback mechanism following accelerated clearance of T4 and the rise of TSH is responsible for thyroid overstimulation that leads to formation of thyroid neoplasms. The soft tissue tumours of male mice are brought about by fighting (a paradoxical reaction) and subsequent initiation by encrustation and foreign body reaction. The increased incidence of pulmonary adenocarcinomas in female mice may be regarded as fortuitous ("chance finding"), but there is not enough data available to exclude some other mechanisms.

No comparable endocrine changes were observed in man given the therapeutic dose of zopiclone (7.5 mg). The tumour producing dose of zopiclone represents 800 times and the no effect level 80 times the proposed human dose (0.125 mg/kg).

Mutagenicity

Zopiclone and its metabolic products were tested for mutagenic potential in the following assays:

Assay	Indicator species or organism	Doses used
Ames' test	<i>Salmonella typhimurium</i> (TA98, TA100, TA1535, TA1537 & TA 1538) <i>Escherichia coli</i> (WP2 uvrA)	Up to 500 mcg/plate with and without rat liver microsome activating enzymes.
Ames' test	<i>Salmonella typhimurium</i> (5 strains as above)	Concentrated urine extracts from rats treated at 1, 10 and 100 mg/kg for 20 days.

Assay	Indicator species or organism	Doses used
Ames' test	<i>Salmonella typhimurium</i> (5 strains as above)	Up to 5000 mcg/plate with liver microsomal enzymes from B6C3F1 mice.
Ames' test	<i>Salmonella typhimurium</i> (5 strains as above) <i>Escherichia coli</i> (WP2 uvrA)	1) Urine samples from volunteers receiving 7.5, 10 or 15 mg with or without liver microsomal enzymes. 2) Two major metabolites, N-oxide and N-desmethyl derivatives: up to 1000 mcg per plate.
<i>In vitro</i> and <i>In vivo</i> host mediated assay	<i>Saccharomyces cerevisiae</i> (D7)	<i>In vitro</i> : up to 1000 mcg/mL <i>In vivo</i> , in mice: 100 mg/kg PO
Gene forward mutation test	Chinese Hamster Ovary cells (CHO/HG PRT)	Up to 200 mcg/mL with or without metabolic activation.
<i>In vitro</i> mammalian cell test for clastogenicity.	Chinese Hamster Ovary cells (CHO/K1 line)	Up to 200 mcg/mL with or without metabolic activation.
DNA repair assay (William's test)	Primary cultures of rat hepatocytes	Up to 10 ⁻⁴ M.
Dominant lethal test	Rats and mice	Up to 120 mg/kg/day PO
Micronucleus test	Mice	Up to 630 mg/kg/day PO
Sex-linked recessive lethal test	<i>Drosophila melanogaster</i> cells (CHO/HG PRT)	2% solution PO activation

All tests were negative. Zopiclone was neither a mutagen nor a clastogen and did not give rise to mutagenic metabolites either in experimental animals or in man.

Reproduction and Teratology

1. Fertility and general reproductive performance

The effect of zopiclone was evaluated in three studies. First, treated male rats were mated with treated female rats, the oral doses of zopiclone being 0, 2, 12 and 120 mg/kg. The males were treated for 10 weeks prior to mating, the females for 2 weeks prior to mating, during pregnancy and throughout a 3-week lactation period. In two further experiments, treated males (120 mg/kg) were mated with untreated females and untreated males were mated with treated females (120 mg/kg). Both of the latter experimental conditions included a control group.

Rate of pregnancy, number of implantations, rate of resorption and number of live fetuses were similar in control and low and medium dose-treated rats. However, mortality of pups was significantly higher in the mid dose group than in the control group.

At the 120 mg/kg dose, regardless whether treated males were mated with treated or untreated females, only ~10% of the females became pregnant and even in these animals resorption was complete. When high dose-treated females were mated with untreated males, the rate of pregnancy was only slightly lower than in controls (83% vs 100%) and all pregnant females

delivered live fetuses. Survival of fetuses, up to day 21 of lactation, was significantly lower than in controls.

In conclusion, a 120 mg/kg dose of zopiclone induces sterility in male animals, while in females it affects pregnancy rate only slightly. Up to 12 mg/kg, the drug does not affect fertility and reproductive functions.

2. Teratology – rats

The study was performed in groups of 20 rats each, given zopiclone orally at doses of 0, 5, 25 and 125 mg/kg from day 5 to day 15 of gestation. In rats treated with the high dose of zopiclone, the following changes were seen when compared to the controls: food intake and final body weight (day 20) were slightly but significantly lower, the rate of resorption was somewhat higher (9% vs 6%) and the mean weight of live fetuses slightly but significantly lower (3.5 g vs 3.7 g). One pup had a sternal malformation, and five pups from the same mother had asymmetrical sternbrae. Both anomalies occur in the strain used. In conclusion, zopiclone is not teratogenic in rats in doses up to 125 mg/kg.

3. Teratology – rabbits

The study was performed in groups of 16 rabbits each given zopiclone orally at doses of 0, 5, 25 and 125 mg/kg from day 6 to day 16 of gestation. Food intake and weight gain were significantly affected and in a dose-related manner. At the 125 mg/kg dose, the rabbits actually lost some weight by the end of treatment. The mean weight of live fetuses in this group was significantly lower than in the controls (31.5 g vs 35.8 g). Three of the fetuses were malformed, 1/109 live fetuses in the mid dose and 2/129 live fetuses in the high dose, exhibiting malformations of the urinary tract, exencephaly and forelimbs with clubfeet and malformations of the large heart vessels, respectively. These malformations do occur in the strain used. In conclusion, zopiclone is not teratogenic in rabbits in doses up to 125 mg/kg.

4. Perinatal and postnatal study

This was a two generation study in which male and female offsprings (F₁ generation) of treated mothers were bred and the F₂ generation also observed.

Zopiclone was given orally at doses of 0, 10, 50 and 250 mg/kg from day 17 of gestation to day 28 of lactation. The following significant changes were observed: smaller litter size in the high dose group, lower body weights at birth and at weaning in the mid and high dose groups, dose-related increase of mortality at birth and between days 1 and 28. Mortality during lactation was significantly different from control even in the 10 mg/kg group. Cannibalization of pups increased in a dose-related manner; this effect might have been due to the fact that the pups were sedated, hypothermic and had problems with suckling.

Gross behaviour, physical development, auditory function, spontaneous motor activity and learning behaviour were normal in the surviving F₁ pups. Males and females from the F₁ generation mated successfully except for three rats which were infertile (one male rat from the 50 mg/kg group and one male and one female rat from the 250 mg/kg group). The male rat from

the mid dose group had bilateral hypoplastic testes and epididymis. Mortality and weights of the F₂ generation were within the normal range for the strain used. One F₂ pup, from the mid dose group, had oligodactyly with syndactyly of the left forelimb.

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PART III: CONSUMER INFORMATION

**Pr Sandoz Zopiclone
Zopiclone tablets**

This leaflet is part III of a three-part "Product Monograph" published when Sandoz Zopiclone was approved for sale in Canada and is designed specifically for Consumers. Please read this information before you start to take your medicine. Keep this leaflet until you have finished all your tablets, as you may need to read it again. This leaflet should not replace a discussion between you and your doctor about the risks and benefits of Sandoz Zopiclone. This leaflet is a summary and will not tell you everything about Sandoz Zopiclone. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

Sandoz Zopiclone (zopiclone) is a prescription medication intended to help you sleep if you have transient and short-term insomnia. Symptoms of insomnia may vary: you may have difficulty in falling asleep, or awaken often during the night, or awaken early in the morning, or you may have all three symptoms.

Treatment with Sandoz Zopiclone should usually not go on for more than 7-10 days and should be restricted for insomnia where disturbed sleep results in impaired daytime functioning. Sandoz Zopiclone does not treat the underlying cause of your insomnia.

What it does:

Sandoz Zopiclone 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 Sandoz Zopiclone if you have:

- a muscular disease known as myasthenia gravis
- a severe hepatic insufficiency (liver problems)
- severe lung or respiratory disease, including sleep apnea.
- a known allergy to zopiclone or any of the ingredients Sandoz Zopiclone contains (see **What the nonmedicinal ingredients are**).

What the medicinal ingredient is:

The active ingredient in Sandoz Zopiclone is zopiclone.

What the non-medicinal ingredients are:

Sandoz Zopiclone (zopiclone) 5.0 mg tablets contains: calcium phosphate dihydrate, cornstarch, hydroxypropyl methylcellulose, lactose, magnesium stearate, maltodextrin, polydextrose, polyethylene glycol, sodium croscarmellose, titanium dioxide and triacetin.

Sandoz Zopiclone (zopiclone) 7.5 mg tablets contains: calcium phosphate dihydrate, cornstarch, D&C yellow no.10 aluminum lake, FD&C blue no.1 aluminum lake, FD&C blue no.2 aluminum lake, hydroxypropyl methylcellulose, lactose, magnesium stearate, maltodextrin, polydextrose, polyethylene glycol, sodium croscarmellose, titanium dioxide and triacetin.

What dosage forms it comes in:

Tablets, 5.0 mg and 7.5 mg.

WARNINGS AND PRECAUTIONS

Complex sleep-related behaviours

There have been reports of people getting out of bed while not fully awake after taking Sandoz Zopiclone 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 Sandoz Zopiclone 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 Sandoz Zopiclone than prescribed.
2. Do not take Sandoz Zopiclone if you drink alcohol.
3. Talk to your doctor 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 Disorder (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 Sandoz Zopiclone 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.

Mental Alertness: Sandoz Zopiclone may affect your ability to be alert the next day. **DO NOT DRIVE A CAR** or operate potentially dangerous machinery:

- If you do not feel fully awake

- If it has not been at least 12 hours since taking the medicine, even if you feel fully awake, especially in elderly patients and in patients who take the 7.5 mg dose
- In all cases, until you experience how the drug affects you the next day.

Memory problems: Sandoz Zopiclone 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 Sandoz Zopiclone** 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 Sandoz Zopiclone, 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, agitation, irritability, illusions, nightmares, hallucinations, delusion (a false belief or wrong judgment, held with conviction despite evidence to the contrary), 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 Sandoz Zopiclone, discuss the matter immediately with your doctor.

Worsening of Side Effects

DO NOT CONSUME ALCOHOL WHILE TAKING Sandoz Zopiclone. Some medicines may also worsen side effects that some patients experience with Sandoz Zopiclone (see **Drug Interactions with this medication**).

Elderly: An increased risk of falls and fractures has been reported in elderly people who take sleeping pills such as Sandoz Zopiclone.

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 Sandoz Zopiclone 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 Sandoz Zopiclone** at anytime during pregnancy, it may affect the developing baby.

Use in Nursing Mothers: Sandoz Zopiclone 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 Sandoz Zopiclone talk to your doctor or pharmacist if:

- You have a lung disease or breathing problems.
- You have liver or kidney condition.
- You have a history of depression and/or suicide thoughts or attempts.
- You have had unexpected reactions to alcohol or sedative medications in the past, such as irritability, aggression, hallucinations, etc.
- You have a history of drug or alcohol abuse or addiction.
- You are planning to become pregnant, if you are pregnant, or if you become pregnant while taking this medication.
- You are breastfeeding.
- You consume alcohol.

- You are taking any other medicines, including over-the counter medicines and herbal products.
- You have lactose intolerance.

INTERACTIONS WITH THIS MEDICATION

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

Zopiclone 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 Sandoz Zopiclone 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

Zopiclone is an effective medication and is relatively free of serious problems when used for the short-term management of insomnia. Sleeplessness may last only for a short time and may respond to brief treatment. The risks and benefits of prolonged use should be discussed with your doctor.

Usual dose:

Sandoz Zopiclone should be taken just before retiring for the night.

Adult: The recommended starting dose is 3.75 mg (one half of a 7.5 mg tablet). This can be increased to 5 mg or 7.5 mg if advised by your doctor.

Special population: Elderly (65 years of age or more), debilitated patients and/or patients with liver, kidney, or chronic respiratory problems should start with 3.75 mg (one-half of a 7.5 mg tablet) at bedtime just before retiring. The dose in elderly, debilitated patients and/or patients with liver or kidney problems is not to exceed 5 mg.

Follow your doctor's advice about how to take Sandoz Zopiclone, when to take it, and how long to take it.

The lowest effective dose should be used.

Do not increase the prescribed dose of Sandoz Zopiclone.

Do not take Sandoz Zopiclone if it is not prescribed for you.

Treatment with Sandoz Zopiclone should usually not exceed 7-10 consecutive days. **Do not take Sandoz Zopiclone** for more than 7-10 days without first consulting your doctor. If you still have problems sleeping after you finish your tablets, contact your doctor again.

Do not take Sandoz Zopiclone if you drink alcohol.

Sandoz Zopiclone is not indicated for patients under 18 years of age. **Do not take Sandoz Zopiclone if you are under 18 years of age.**

Do not take Sandoz Zopiclone when a full night's sleep is not possible before you would again need to be active and functional.

Do not drive a car or operate potentially dangerous machinery until you experience how this drug will affect you the next day (see WARNINGS AND PRECAUTIONS, Patients requiring mental alertness).

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms. Show the doctor your bottle of tablets.

Missed Dose:

Sandoz Zopiclone should be taken at bedtime just before retiring for the night. If you miss a dose, wait and take your next dose at your regular time. Do not take 2 doses at the same time. Do not make up for a missed dose

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Common Side Effects:

The most common adverse reaction seen with Sandoz Zopiclone is taste alteration (bitter taste).

Sandoz Zopiclone may cause drowsiness, dizziness, lightheadedness, and difficulty with coordination. Users must be cautious about engaging in hazardous activities requiring complete mental alertness, e.g., operating machinery or driving a motor vehicle. This risk is increased by concomitant intake of alcohol.

How sleepy you are the day after you use one of these sleeping pills depends on your individual response and on how quickly your body gets rid of the medication. The larger the dose, the more likely that you will experience drowsiness, etc., the next day. It is important that you comply with the dose your physician has prescribed. If you experience excessive drowsiness the next

day that affects your ability to perform tasks in the morning contact your physician as your dose may need to be reduced (see Warnings and Precautions, Patients requiring mental alertness).

Elderly patients are especially susceptible to side effects. Excessive drowsiness in the elderly may result in falls and fractures.

Do not drink alcohol while using Sandoz Zopiclone. Do not use sleeping pills along with other medications without first discussing this with your doctor.

Withdrawal-related side effects: You may experience an increase in sleep difficulties (rebound insomnia) and/or “increased daytime anxiety” (rebound anxiety) for one or two days after discontinuing Sandoz Zopiclone (see **Warnings and Precautions, Drug abuse, dependence and withdrawal**).

Allergic reactions:

Rare cases of severe allergic reactions have been reported. Symptoms may include:

- swelling of the tongue or throat, trouble breathing, nausea and vomiting. Get emergency medical help if you get these symptoms after taking Sandoz Zopiclone

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect	Talk with your doctor or pharmacist		Seek urgent medical attention	
	Only if severe	In all cases		
Uncommon	Unexpected reactions such as excitement, agitation, hyperactivity, hallucination, worsened insomnia, aggression, irritability, rages, psychoses, and violent behaviour	✓		
	Depressed Mood		✓	
	Severe allergic reactions (swelling of the tongue or throat, trouble breathing, nausea and vomiting)			✓
	Withdrawal effects (abdominal and muscle cramps, vomiting, sweating, tremor, and very rare cases of convulsions)			✓
Rare	Somnambulism (sleepwalking)- getting out of bed while not fully awake and do activities you do not remember the day after		✓	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect	Talk with your doctor or pharmacist		Seek urgent medical attention	
	Only if severe	In all cases		
Very rare	Thoughts of death or suicide		✓	
Unknown	Trouble breathing		✓	

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

Reporting Side Effects
 You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at [MedEffect](#);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
 - Fax to 1-866-678-6789 (toll-free), or
 - Mail to: Canada Vigilance Program
 Health Canada, Postal Locator 0701E
 Ottawa, ON
 K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at [MedEffect](#).

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.

HOW TO STORE IT

Store in a dry place, at room temperature (15° - 30°C). Protect from light. Do not exceed the expiry date indicated on the container.

Keep out of the reach of children.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:

<http://www.sandoz.ca> or by contacting the sponsor, Sandoz Canada Inc., at:
1-800-361-3062

or by written request at:

145, Jules-Léger
Boucherville QC
J4B 7K8

or by e-mail at :

medinfo@sandoz.com

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