PRODUCT MONOGRAPH

NU-ZOPICLONE

Zopiclone Tablets

5 mg and 7.5 mg

Hypnotic

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PRODUCT MONOGRAPH

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5 mg and 7.5 mg

THERAPEUTIC CLASSIFICATION

Hypnotic

ACTIONS AND CLINICAL PHARMACOLOGY

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

In sleep laboratory studies of 1 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) and beta (elimination) 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).

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

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.

Some manifestations of rebound insomnia have been reported both in sleep laboratory and clinical studies following the withdrawal of zopiclone.

Zopiclone treatment was associated with dose-related residual effects (see 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 [$t_{½}$]**:** 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.

Metabolism: Zopiclone is extensively metabolized by three major pathways; only about 4 to 5% of the drug is excreted unchanged in the urine. 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 C^{14}-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 PATIENT POPULATION

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).

Patients with Mild to Moderate Renal Insufficiency: The pharmacokinetics of zopiclone were not affected. 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.

COMPARATIVE BIOAVAILABILITY

A comparative bioavailability study was performed using healthy human volunteers. The rate and extent of absorption of zopiclone following administration of a single 7.5 mg (one tablet) oral dose of either NU-ZOPICLONE or IMOVANE were measured and compared. The results from measured data are summarized as follows:

Summary Table of the Comparative Bioavailability Data Zopiclone (Dose: 7.5 mg) From Measured Data			
Parameter	Geometric Mean Arithmetic Mean (CV%)		*Ratio of Means (%)
	Nu–Zopiclone	Imovane†	
AUC_T (ng•hr/mL)	382 386 (16)	387 391 (16)	99.2
AUC_I (ng•hr/mL)	408 412 (15)	412 416 (15)	99.5
C_{max} (ng/mL)	67.5 68.6 (18)	65.9 66.7 (16)	102.3
T_{max} (hr)*	1.13 (43)	1.17 (66)	-
$t_{1/2}$ (hr)	4.54 (18)	4.59 (17)	-

The T_{max} and $t_{1/2}$ parameters are expressed as the arithmetic means.

* Based on the least squares estimate of the geometric mean.

† Imovane (Rhone-Poulenc Rorer Canada Inc.) was purchased at a Canadian retail pharmacy.

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.

NU-ZOPICLONE (zopiclone) is indicated for the symptomatic relief of transient and short-term insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakenings.

Treatment with NU-ZOPICLONE should usually not exceed 7- 10 consecutive days. Use for more than 2-3 consecutive weeks requires complete re-evaluation of the patient. Prescriptions

for NU-ZOPICLONE 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.

CONTRAINDICATIONS

NU-ZOPICLONE (zopiclone) is contraindicated in patients with known hypersensitivity to the drug or any component of its formulation, and those with severe impairment of respiratory function, e.g. sleep apnea syndrome.

NU-ZOPICLONE is contraindicated in patients who in the past manifested paradoxical reactions to alcohol and/or sedative medications.

WARNINGS

GENERAL

NU-ZOPICLONE (zopiclone) should be used with caution in patients who in the past manifested paradoxical reactions to alcohol and/or sedative medications.

The smallest possible effective dose should be prescribed for elderly patients. Inappropriate, heavy sedation in the elderly may result in accidental events/falls.

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.

NU-ZOPICLONE should be used with caution in patients who have myasthenia gravis or severe hepatic insufficiency.

Pregnancy

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 NU-ZOPICLONE (zopiclone) during pregnancy is not recommended. If NU-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 a benzodiazepine hypnotic has resulted in neonatal CNS depression due to transplacental distribution. Similar effects can be expected to occur with zopiclone, due to its pharmacological effects.

Memory Disturbance

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 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. 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.

Abnormal Thinking and Psychotic Behavioural Changes

Abnormal thinking and psychotic behavioural changes have been reported to occur in association with the use of benzodiazepines and benzodiazepine-like agents including zopiclone, although rarely. Some of the changes may be characterized by decreased inhibition, e.g., aggressiveness 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 bizarre behaviour, hallucinations, and depersonalization. Abnormal behaviour 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 behaviors 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.

Confusion

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 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.

PRECAUTIONS

DRUG INTERACTIONS

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

Compounds which inhibit certain hepatic enzymes (particularly cytochrome P450) may enhance the activity of benzodiazepines and benzodiazepine-like agents. Examples include cimetidine or erythromycin.

Drug Abuse, Dependence and Withdrawal

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.

The risk of dependence is increased in patients with a history of alcoholism, 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.

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

Patients with Specific Conditions

Zopiclone should be given with caution to patients with impaired hepatic or renal function, or severe pulmonary insufficiency. Respiratory depression has been reported in patients with compromised respiratory function.

Patients Requiring Mental Alertness

Because of zopiclone's CNS depressant effect, 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.

Use in Pregnancy

For teratogenic effects see WARNINGS.

Non-teratogenic effects: a child born to a mother who is on benzodiazepines or benzodiazepine-like agents may be at risk for withdrawal symptoms from the drug during the postnatal period.

Use in Nursing Mothers

Zopiclone is excreted in human milk, and its concentration may reach 50% of the plasma levels. Therefore, the administration of zopiclone to nursing mothers is not recommended.

Use in Children

The safety and effectiveness of zopiclone in children and young adults below the age of 18 has not been established.

Use in Elderly

Elderly patients are especially susceptible to dose-related adverse effects, such as drowsiness, dizziness, or impaired coordination. Inappropriate, heavy sedation may result in accidental event/falls. Therefore, the lowest possible dose should be used in these subjects.

ADVERSE REACTIONS

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.

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 *italics.*

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

Cardiovascular: palpitations.

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

Respiratory: dyspnea.

Special Senses: amblyopia.

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

Metabolic and Nutritional: weight loss.

Others: *bitter taste,* headache, limb heaviness, chills.

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

Geriatric Patients: Geriatric patients tended to have a higher incidence of palpitations, vomiting, anorexia, sialorrhea, confusion, agitation, anxiety, tremor and sweating than younger patients.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

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.

Full manifestation of zopiclone overdosage can be expected to be consistent with its pharmacological activity, i.e., somnolence, confusion and coma with reduced or absent reflexes.

Treatment should be supportive and in response to clinical signs and symptoms. Respiration, pulse and blood pressure should be monitored and supported by general measures when necessary. Immediate gastric lavage should be performed. Intravenous fluid should be administered and an adequate airway maintained. Hemodialysis is probably of no value. It should be borne in mind that multiple agents may have been ingested.

The benzodiazepine antagonist flumazenil (Anexate®), is a specific antidote in known or suspected overdose with benzodiazepines or benzodiazepine like agents. (For conditions of use see Anexate® Product Monograph).

DOSAGE AND ADMINISTRATION

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

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

Adult Dose: The usual adult dosage is 5.0 mg to 7.5 mg. The 7.5 mg dose should not be exceeded (see PRECAUTIONS).

Geriatric Patients: In the elderly and/or debilitated patient, an initial dose of 3.75 mg at bedtime is recommended. The dose may be increased to 5.0 or 7.5 mg if the starting dose does not offer adequate therapeutic effect.

Patients with Impaired Liver Function or Chronic Respiratory Insufficiency: The recommended dose is 3.75 mg depending on acceptability and efficacy. Up to 7.5 mg may be used with caution in appropriate cases.

NU-ZOPICLONE 7.5 mg tablets may be divided at the scoreline to provide a 3.75 mg dose.

NU-ZOPICLONE is not indicated for patients under 18 years of age.

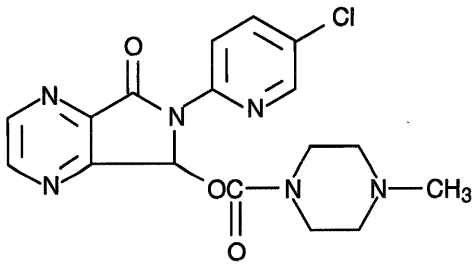
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Proper/Common Name: Zopiclone

Chemical Name: 4-methyl-1-piperazinecarboxylic acid ester with 6-(5-chloro-2-pyridyl)-6,7-dihydro-7-hydroxy-5H-pyrrolo[3,4-b]pyrazin-5-one

Structural Formula:



Molecular Formula: $C_{17}H_{17}ClN_6O_3$

Molecular Weight: 388.82

Description: Fine white odorless non hygroscopic powder. Melting point: 178˚C. Zopiclone is freely soluble in chloroform and methylene chloride, soluble in dimethylformamide and 0.1 N hydrochloric acid, slightly soluble in acetone and practically insoluble in water, ethanol and ethyl ether.

Composition

NU-ZOPICLONE 5 mg: In addition to zopiclone, each film-coated tablet contains the non-medicinal ingredients magnesium stearate, lactose monohydrate, microcrystalline cellulose, hydroxypropyl methylcellulose, polyethylene glycol, titanium dioxide.

NU-ZOPICLONE 7.5 mg: In addition to zopiclone, each film-coated tablet contains the non-medicinal ingredients magnesium stearate, lactose monohydrate, microcrystalline cellulose, hydroxypropyl methylcellulose, polyethylene glycol, titanium dioxide, D&C yellow #10, and FD&C blue #1.

Stability and Storage Recommendations

Store at room temperature 15-30^{o}C. Protect from light.

AVAILABILITY OF DOSAGE FORMS

NU-ZOPICLONE 5 mg: Each round, white, plain, biconvex film-coated tablet contains zopiclone 5 mg. Available in bottles of 100 and 1000 tablets.

NU-ZOPICLONE 7.5 mg: Each oval, blue, biconvex, film-coated, scored tablet engraved ‘7.5’ on one side contains zopiclone 7.5 mg. Available in bottles of 100 and 500, unit dose packages of 100 (10x10), and Nu-Pharm Long-Term Care unit dose packages (Nu-LTC Paks) of 620 (20x31) and 700 (20x35) tablets.

INFORMATION TO THE PATIENT

FACTS ON NU-ZOPICLONE (Zopiclone Tablets)

INTRODUCTION

NU-ZOPICLONE is intended to help you sleep. It is one of several prescription sleeping pills that have generally similar properties.

If you are prescribed one of these medications, you should consider both their benefits and risks. Important risks and limitations include the following:

– the medication may cause dependence,

– the medication may affect your mental alertness or memory, particularly when not taken as prescribed.

In order to guide you in the safe use of the product, this leaflet will inform you about this class of medication in general, and about NU-ZOPICLONE in particular.

BUT THIS LEAFLET SHOULD NOT REPLACE A DISCUSSION BETWEEN YOU AND YOUR DOCTOR ABOUT THE RISKS AND BENEFITS OF NU-ZOPICLONE.

Safe Use of NU-ZOPICLONE

– NU-ZOPICLONE is a prescription medication, intended to help you sleep. Follow your doctor's advice about how to take NU-ZOPICLONE, when to take it, and how long to take it. DO NOT TAKE NU-ZOPICLONE if it is not prescribed for you.

– DO NOT TAKE NU-ZOPICLONE for more than 7-10 days without first consulting your doctor.

– DO NOT TAKE NU-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.

– DO NOT TAKE NU-ZOPICLONE at any time during pregnancy. Tell your doctor if you are planning to become pregnant, if you are pregnant, or if you become pregnant while taking this medication.

– Tell your doctor about any alcohol consumption (present or past) or any medicine you are taking now, including drugs you can buy without a prescription. DO NOT CONSUME ALCOHOL WHILE TAKING NU-ZOPICLONE.

– DO NOT INCREASE THE PRESCRIBED DOSE.

– DO NOT DRIVE A CAR or operate potentially dangerous machinery until you experience how this drug will affect you the next day.

– If you develop any unusual disturbing thoughts or behavior while using NU-ZOPICLONE, discuss the matter immediately with your doctor.

– You may experience an increase in sleep difficulties (rebound insomnia) and/or "increased daytime anxiety" (rebound anxiety) for one or two days after discontinuing NU-ZOPICLONE.

EFFECTIVNESS OF NU-ZOPICLONE

NU-ZOPICLONE is an effective medication and is relatively free of serious problems when used for the short-term management of 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.

Insomnia 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.

SIDE EFFECTS

Common Side Effects: NU-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.

Avoid alcohol while using NU-ZOPICLONE. DO NOT USE NU-ZOPICLONE along with other medications without first discussing this with your doctor.

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. Prescription sleeping pills which are eliminated rapidly tend to cause less drowsiness the next day, but may cause withdrawal problems the day after use (see below).

SPECIAL CONCERNS

Memory Problems: NU-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 "traveler's amnesia".

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 NU-ZOPICLONE, you may awake 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 behavior, restlessness, illusions, 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 underlying illness, or are simply spontaneous happenings. In fact, worsened insomnia may in some cases be associated with illnesses that were present before the medication was used.

Important Note

Regardless of the cause, if you take these medications, report any mental or behavioural changes promptly to your doctor.

Effects on Pregnancy

Certain benzodiazepines sleeping pills have been linked to birth defects when taken during the early months of pregnancy. It is not yet known if NU-ZOPICLONE (zopiclone) could cause similar effects. In additions, sleeping pills taken during the last weeks of pregnancy have been known to sedate the baby. Therefore, **AVOID USING THIS MEDICATION DURING PREGNANCY.**

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.

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 ED_{50}'s are similar in naive and zopiclone-treated animals.

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 ^{3}H-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, α1 and α2 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.

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.

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 i.v. 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.

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 TOXICOLOGY

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	i.v.	450
	i.p.	580
	p.o.	1150
Rats	p.o.	2300
Dogs	p.o.	≥4500
	i.v.	400
Cats	p.o.	>1500
Rabbits	p.o.	~2500
Monkeys	p.o.	>4500

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

LONG-TERM TOXICITY STUDIES

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.

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-dependent 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. T_4 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, 100 mg/kg/day for two years. There was an increased incidence of mammary tumors with a shift toward more anaplastic forms in female and an increase of thyroid tumors 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 tumors.

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 tumors and the shift from well differentiated to poorly differentiated mammary carcinomas. The altered feedback mechanism following accelerated clearance of T_4 and the rise of TSH is responsible for thyroid over stimulation that leads to formation of thyroid neoplasms. The soft tissue tumors 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 tumor-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	*Salmonella typhimurium* (TA98, TA100, TA1535, TA1537 & TA1538) *Escherichia coli* (WP2 uvrA)	Up to 500 mcg/plate with and without rat liver microsome activating enzymes.
Ames' test	*Salmonella typhimurium* (5 strains as above)	Concentrated urine extracts from rats treated at 1, 10 and 100 mg/kg for 20 days.
Ames' test	*Salmonella typhimurium* (5 strains as above)	Up to 5000 mcg/plate with liver microsomal enzymes from B6C3F1 mice.
Ames' test	*Salmonella typhimurium* (5 strains as above) *Escherichia coli* (WP2 uvrA)	1. Urine samples from volunteers receiving 7.5, 10 or 15 mg zopiclone, with or without liver microsomal enzymes. 2. Two major metabolites, the N-oxide and N-desmethyl derivatives: up to 1000 mcg/plate.
In vitro and in vivo host mediated assay	*Saccharomyces cerevisiae* (D7)	In vitro: up to 1000 mcg/mL In vivo, in mice: 100 mg/kg p.o.
Gene forward mutation test	Chinese Hamster Ovary cells (CHO/HG PRT)	Up to 200 mcg/mL with or without metabolic activation.

ASSAY	INDICATOR SPECIES OR ORGANISM	DOSES USED
In vitro 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 p.o.
Micronucleus test	Mice	Up to 630 mg/kg/day p.o.
Sex-linked recessive lethal test	Drosophila melanogaster cells (CHO/HG PRT)	2% solution p.o. 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

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 of 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.

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 sternebrae. Both anomalies occur in the strain used. In conclusion, zopiclone is not teratogenic in rats in doses up to 125 mg/kg.

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.

Prenatal and Postnatal Study

This was a two-generation study in which male and female offspring (F_1 generation) of treated mothers were bred and the F_2 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 F_1 pups. Males and females from the F_1

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 F_2 generation were within the normal range for the strain used. One F_2 pup from the mid dose group had oligodactyly with syndactyly of the left forelimb.

BIBLIOGRAPHY

1. Aranko K, Henriksson, Hublin C, Seppalainen AM. Misuse of zopiclone and convulsions during withdrawal. Pharmacopsychiat 1991; 24:138-40

2. Autret E, Maillard F, Autret A. Comparison of the clinical hypnotic effects of zopiclone and triazolam. Eur J Clin Pharmacol 1987; 31: 621-623

3. Beaupre A, Soucy R, Phillips R, Bourgouin J. Respiratory center output following zopiclone or triazolam. Eur J Clin Pharmacol 1987; 31: 621-623. diazepam administration in patients with pulmonary disease. Respiration 1988; 54: 235-240.

4. Billiard M, Besset A, Delustrac C, Brissand L. Dose-response effects of zopiclone on night sleep, and on nighttime and daytime functioning. Sleep 1987; 10 (Suppl 1): 27-34.

5. Blanchard JC, Boireau A, Julou L. Brain receptors and zopiclone. Pharmacology 1983; 27 (Suppl 2): 59-69.

6. Blanchard JC, Zundel JL, Julou L. Differences between cyclopyrrolones (suriclone and zopiclone) and benzodiazepines binding to rat hippocampus photolabelled membranes. Biochem Pharmacol 1983;32: 3651-3653.

7. Campbell RD, Grace MGA, Bourgouin J, Forget JR Efficacy and safety of zopiclone in the treatment of insomnia. Curr Ther Res 1987; 42 665-670.

8. Diagnostic Classification Steering Committee. THORPE MJ, Chairman International Classification of Sleep Disorders: Diagnostic and coding manual Rochester, Minnesota. American Sleep Disorders Association, 1990.

9. Dorian P, Sellers EM, Kaplan H, Hamilton C. Evaluation of zopiclone physical dependence liability in normal volunteers. Pharmacology 1983; 27 (Suppl 2): 226-234.

10. Dreyfus JF Zopiclone - Clinical efficacy and tolerance Symposium on zopiclone. Tokyo (Japan), July 17, 1981, pp: 103-117.

11. Elie R. A controlled dose-response study of zopiclone in normal insomnia. Symposium on zopiclone. Tokyo (Japan), July 17, 1981, pp: 149-153.

12. Elie R, Deschesnes JR Efficacy and tolerance of zopiclone in insomniac geriatric patients. Pharmacology 1983; 27 (Suppl 2): 179-187.

13. Fleming JA, McClure DJ, Mayes C, Phillips R, Bourgouin J. A comparison of the efficacy, safety and withdrawal effects of zopiclone and triazolam in the treatment of insomnia. Int Clin Psychopharmacol 1990; 5 (Suppl 2): 29-37

14. Fleming JAE, Bourgouin J, Hamilton P. A sleep laboratory evaluation of the long-term efficacy of zopiclone. Can J Psychiat 1988; 33: 103-107.

15. Fontaine R, Beaudry P, Le Morvan P, Beauclair L, Chouinard G. Zopiclone and triazolam in insomnia associated with generalized anxiety disorder: a placebo-controlled evaluation of efficacy and daytime anxiety. Int Clin Psychopharmacol 1990; 5 (Suppl 2): 173-183

16. Fossen A, Godlibsen OB, Loyning Y, Dreyfus JF. Effects of hypnotics on memory. Pharmacology 1983; 27 (Suppl 2): 116-126.

17. Gaillot J, Decouvalaere B, Marlard M, Smith G, Dreyfus JF. Metabolism of zopiclone. Zopiclone Symposium - "Zopiclone: A Reappraisal". VII World Congress of Psychiatry, Vienna (Austria), July 11-16,1983

18. Gaillot J, Le Roux Y, Houghton GW, Dreyfus JF. Critical factors for pharmacokinetics of zopiclone in the elderly and in patients with liver and renal insufficiency. Sleep 1987; 10 (Suppl 1): 7-21.

19. Goa KL, Heel RC. Zopiclone. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy as an hypnotic. Drugs 1986 32 48-65

20. Griffiths AN, Jones DM, Richens A. Zopiclone produces effects on human performance similar to flurazepam, lormetazepam and triazolam. Br J Clin Pharmac 1986; 21: 647-653.

21. Hayoun G, Bagot C. Comparative efficacy and safety of triazolam and zopiclone in insomniacs seen in general practice. Curr Ther Res 1989; 46:1236-1244.

22. Jovanovic UJ, Dreyfus JF. Polygraphical sleep recordings in insomniac patients under zopiclone or nitrazepam. Pharmacology 1983; 27 (Suppl 2): 136-145.

23. Julou L Pharmacological and toxicological studies on zopiclone. Symposium on zopiclone. Tokyo (Japan), July 17, 1981, pp.9-25

24. King DJ. Benzodiazepines, amnesia and sedation: theoretical and clinical issues and controversies. Human Psychopharmacol 1992; 7 79-87

25. Lader M, Freka G. Subjective effects during administration and on discontinuation of zopiclone and temazepam in normal subjects. Pharmacopsychiatry 1987; 20: 67-71.

26. Lader M, Denney SC. A double-blind study to establish the residual effects of zopiclone on performance in healthy volunteers. Pharmacology 1983 27 (Suppl 2): 96-108.

27. Lamphere JK, Roehrs TA, Zorick FJ, Koshorek G, Roth T. The dose effects of zopiclone Human Psychopharmacol 1989; 4: 41-46.

28. Maczaj M. Pharmacological treatment of insomnia. Drugs 1993; 45: 44-55

29. Mamelak M, Csima A, Price V. Effects of zopiclone on the sleep of chronic insomniacs. Pharmacology 1983; 21 (Suppl 2): 156-164.

30. Mamelak M, Buck L, Csima A, Price V, Smiley A. Effects of flurazepam and zopiclone on the performance of chronic insomniac patients: a study of ethanol-drug interaction. Sleep 1987; 10 (Suppl 1): 79-87.

31. Marc-Aurele J, Caille G, Bourgoin J. Comparison of zopiclone pharmacokinetics in patients with impaired renal function and normal subjects. Effects of hemodialysis. Sleep 1987 10 (Suppl 1): 22-26.

32. Monchesky TC, Billings BJ, Phillips R. Zopiclone: A new nonbenzodiazepine hypnotic used in general practice. Clin Ther 1986; 8: 283-291.

33. Monchesky TC, Billings BJ, Phillips R, Bourgouin J. Zopiclone in insomniac shiftworkers. Int Arch Occup Environ Health 1989; 61: 255-259.

34. Nair NPV, Schwartz G, Dimitri R, Le Morvan P, Thavundayil JX. A dose-range finding study of zopiclone in insomniac patients. Int Clin Psychopharmacol 1990; 5 (Suppl 2): 1-10.

35. Nicholson AN, Stone B. Zopiclone: sleep and performance studies in healthy man. Pharmacology 1983; 27 (Suppl 2): 92-97.

36. O'Hanlon JF, Volkerts ER, Louwerens JW, Gloerich ABM, Brookhuis KA. Zopiclone's residual effect upon actual driving performance versus those of nitrazepam and flunitrazepam. Clin Neuropharmacol 1984; 7 (Suppl 1): 620-621.

37. Pecknold J, Wilson R, LeMorvan R Long-term efficacy and withdrawal of zopiclone: a sleep laboratory study. Int Clin Psychopharmacol 1990; 5 (Suppl 2): 57-67.

38. Ranlov PJ, Nielsen SR The effect of zopiclone and diazepam on ventilatory responses in normal human subjects. Sleep 1987; 10 (Suppl 1): 40-47.

39. Roberts CJC, Parker G. The pharmacokinetics and pharmacodynamics of zopiclone in cirrhotic patients. Zopiclone symposium, 'Zopiclone: the third generation of hypnotics' IV International Congress of Sleep Research (A.P.S.S.), Bologna, Italy, July 18-22,1983.

40. Seppala T, Dreyful JF, Saario I, Nuotto E. Zopiclone and flunitrazepam in healthy subjects: hypnotic activity, residual effects on performance and combined effects with alcohol. Drugs Exp Clin Res 1982; 8: 35-47.

41. Subhan Z, Hindmarch I. Effects of zopiclone and benzodiazepine hypnotics on search in short-term memory. Neuropsychobiology 1984; 12: 244-248.

42. Trifiletti RR, Synder SH. Anxiolytic cyclopyrrolones zopiclone and suriclone bind to a novel site linked allosterically to benzodiazepine receptors Mol Pharmacol 1984; 26 456-469.

43. van der Kleijn E. Effects of zopiclone and temazepam on sleep, behaviour and mood during the day. Eur J Clin Pharmacol 1989; 36: 247-251.

44. Wadworth AN, McTavish D. Zopiclone: a review of its pharmacological properties and therapeutic efficacy as an hypnotic. Drugs & Aging 1993; 3: 441-59

45. Wickstrom E, Godtlibsen OB, Bredesen JE, Jensen MH. Performance and mood following partial sleep deprivation: A randomized, double-blind study of zopiclone, triazolam, flunitrazepam, ethanol and placebo. Hum Psychopharmacol 1988; 3: 3-11.

46. Yanagita T. Dependence potential of zopiclone studied in monkeys. Pharmacology 1983;27 (Suppl 2): 216-227.