

PRODUCT MONOGRAPH

TEMAZEPAM
Temazepam Capsules USP
15 mg and 30 mg

Hypnotic Agent

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PRODUCT MONOGRAPH

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15 mg and 30 mg

THERAPEUTIC CLASSIFICATION

Hypnotic Agent

ACTIONS AND CLINICAL PHARMACOLOGY

Temazepam is a benzodiazepine with hypnotic properties.

Benzodiazepines act as depressants of the central nervous system (CNS). It is believed that benzodiazepines enhance or facilitate the effects of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA).

Benzodiazepines act as agonists at the benzodiazepine receptors sites. The benzodiazepine-GABA receptor-chloride ionophore complex functions mainly in the gating of the chloride channel. Benzodiazepines are thought to produce their pharmacological effects by facilitating GABA-mediated transmission in the CNS, which reportedly increase the frequency of the chloride channel opening.

In sleep laboratory studies, the effect of temazepam 15 and 30 mg, was compared to placebo over a 2-week period. There was a linear dose-response improvement in total sleep time and sleep latency with significant drug-placebo differences occurring for total sleep time at both doses, and for sleep latency at the higher dose. REM sleep was essentially unchanged and slow wave sleep was decreased.

REBOUND INSOMNIA

A transient syndrome, known as "rebound insomnia", whereby the symptoms that led to treatment with a benzodiazepine recur in an enhanced form, may occur on withdrawal of hypnotic treatment. In the sleep laboratory studies, no measurable effects on daytime alertness

or performance occurred following temazepam treatment or during the withdrawal period, even though a transient sleep disturbance in some sleep parameters was observed following the withdrawal of the higher doses.

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. However, during nightly use and for an extended period, pharmacodynamic tolerance or adaptation to some effects of benzodiazepine hypnotics may develop.

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 benzodiazepine hypnotics: 1) increased wakefulness during the last third of the night and 2) the appearance of increased day-time anxiety (see WARNINGS).

PHARMACOKINETICS

Orally administered temazepam is well absorbed in man. In a single and multiple dose absorption, distribution, metabolism and excretion (ADME) study, using ³H-labelled drug, temazepam was found to have minimal (8%) first-pass metabolism. There were no active metabolites formed and the only significant metabolite present in blood was the O-conjugate. Oral administration of 15 to 45 mg temazepam in man resulted in rapid absorption with significant blood levels achieved in 30 minutes and peak levels at 2-3 hours. Drug levels in blood declined in a biphasic manner with a short half-life ranging from 0.4 to 0.6 hour and a terminal half-life from 3.5 to 18 hours (mean 9 hours). The inactive O-conjugate metabolite was formed with a half-life of 10 hours and excreted with a half-life of approximately 2 hours. Thus, O-conjugation is the rate limiting step in the biodisposition. In a multiple dose study, steady-state was approximated after the second daily dose with no evidence of accumulation after 5 consecutive daily doses of 30 mg temazepam. Steady-state plasma levels at 2.5 hours were 382±192 ng/mL.

Approximately 96% of unchanged drug is bound to plasma protein.

Twenty-four hours after a single oral dose of temazepam approximately 80 to 90% of the drug was recovered in urine, primarily as the O-conjugate. Total recovery from feces and urine in single- and multiple-dose studies was approximately 95%, with only 3 to 13% of the radioactivity detectable in feces. Less than 1% of the dose was excreted as unchanged drug or N-desmethyltemazepam. A dose-proportional relationship has been established for the area under the plasma concentration/time curve over the 15 to 30 mg dose range.

At the dose of 30 mg once a day for 8 weeks, no evidence of enzyme induction was found in man.

Comparative Bioavailability

A single-dose, two-way, randomized crossover bioavailability study using 19 normal male volunteers was conducted to evaluate the relative bioavailability of TEMAZEPAM 30 mg Capsules and Restoril® 30 mg Capsules. The mean pharmacokinetic parameters obtained from the study are listed below:

Summary of Results Based on Temazepam Plasma Levels From Measured Data			
Parameter	Geometric Mean Arithmetic Mean (CV%)		Ratio of Means
	TEMAZEPAM	Restoril®†	
AUC _T (ng · hr/mL)	6117 6535 (38)	5851 6269 (38)	105
AUC _I (ng · hr/mL)	6504 6944 (38)	6241 6661 (37)	104
C _{max} (ng/mL)	855 893 (30)	848 878 (26)	101
T _{max} (h)*	1.64 (1.23)	1.82 (1.09)	--
t _{1/2} (h)*	9.94 (3.01)	9.52 (3.28)	--

*Arithmetic means only (standard deviation).

†Restoril® is manufactured by Sandoz Canada Inc., and was purchased in Canada.

INDICATIONS AND CLINICAL USE

Sleep disturbances 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.

TEMAZEPAM (temazepam) 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 TEMAZEPAM 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 TEMAZEPAM 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.

CONTRAINDICATIONS

TEMAZEPAM (temazepam) is contraindicated in patients with a known hypersensitivity to the drug, any component of its formulation, or to other benzodiazepines; myasthenia gravis; sleep apnea syndrome.

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

WARNINGS

GENERAL

Benzodiazepines should be used with extreme caution in patients with a history of substance or alcohol abuse.

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

The failure of insomnia to remit after 7 to 10 days of treatment may indicate the presence of a primary psychiatric and/or medical illness 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.

PREGNANCY

The use of temazepam 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. During the last weeks of pregnancy, ingestion of therapeutic doses of a benzodiazepine hypnotic has resulted in neonatal CNS depression due to transplacental distribution.

If the drug is prescribed to a woman of childbearing 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.

MEMORY DISTURBANCE

Anterograde amnesia of varying severity has been reported following therapeutic doses of benzodiazepines. The event is rare with temazepam. 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 temazepam 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 have been reported to occur in association with the use of benzodiazepines including temazepam, although rarely.

Some of the changes may be characterized by decreased inhibition, e.g., aggressiveness or extroversion that seem 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. Psychotic behavioural changes that have been reported with benzodiazepines include bizarre behaviour, hallucinations, and depersonalization. Abnormal behaviours associated with the use of benzodiazepines 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.

CONFUSION

The benzodiazepines 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 temazepam.

This may be a manifestation of interdose withdrawal due to the short elimination half-life of the drug.

DEPRESSION

Caution should be exercised if temazepam is prescribed to patients with signs or 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.

POTENTIATION OF DRUG EFFECTS

Temazepam may potentiate the effects of other central nervous system depressant drugs such as alcohol, barbiturates, non-barbiturate hypnotics, antihistamines, narcotics, antipsychotic and antidepressant drugs, and anticonvulsants. Therefore, different benzodiazepines should usually not be used simultaneously and careful consideration should be given if other CNS depressants are administered in combination with temazepam. Patients should be advised against the simultaneous use of other CNS depressant drugs and should be cautioned not to take alcohol because of the potentiation of effects that might occur.

PRECAUTIONS

DRUG INTERACTIONS

Temazepam may produce additive CNS depressant effects when coadministered 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.

DRUG ABUSE, DEPENDENCE AND WITHDRAWAL

Withdrawal symptoms, similar in characteristic 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, including temazepam.

The more severe symptoms are usually associated with higher dosages and longer usage, although patients given therapeutic dosages for as few as 1 to 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 more than the lowest dose 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 temazepam treated patients.

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

PATIENTS WITH SPECIFIC CONDITIONS

Temazepam is O-conjugated in the liver and is primarily excreted by the kidney. Hence, temazepam should be given with caution to patients with impaired hepatic or renal function. Temazepam should also be given with caution to patients with severe pulmonary insufficiency: respiratory depression has been reported in patients with compromised respiratory function.

Temazepam should be used with caution in severely depressed patients or those in whom there is any evidence of latent depression; it should be recognized that suicidal tendencies may be present and protective measures may be necessary.

PATIENTS REQUIRING MENTAL ALERTNESS

Because of temazepam'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 temazepam and alcohol or CNS depressant drugs.

PREGNANCY

For teratogenic effects see WARNINGS. Non-teratogenic effects: a child born to a mother who is on benzodiazepines may be at risk for withdrawal symptoms from the drug during the postnatal period. Also, neonatal flaccidity has been reported in an infant born to a mother who had been receiving benzodiazepines.

LACTATION

It is not known whether or not temazepam is excreted in human milk. Therefore, it should not be given to nursing mothers.

CHILDREN

The safety and effectiveness of temazepam in children below the age of 18 have not been established.

USE IN ELDERLY AND DEBILITATED PATIENTS

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 lowest possible dose should be used in these subjects.

Debililitated patients, or those with organic brain syndrome, are prone to CNS depression after even low doses of benzodiazepines and may experience paradoxical reactions to these drugs. Therefore, temazepam should be used only at the lowest possible dose and adjusted when necessary under careful observation, depending on the response of the patient.

Because temazepam is eliminated by O-conjugation, minimal accumulation occurs.

ADVERSE REACTIONS

During controlled clinical trials in which 1076 patients received temazepam at bedtime, the adverse events occurring in 1% or more of patients are listed below.

	Temazepam % Incidence (n=1076)	Placebo % Incidence (n=783)
Drowsiness	9.1	5.6
Headache	8.5	9.1
Fatigue	4.8	4.7
Nervousness	4.6	8.2
Lethargy	4.5	3.4
Dizziness	4.5	3.3
Nausea	3.1	3.8
Hangover	2.5	1.1
Anxiety	2.0	1.5
Depression	1.7	1.8
Dry mouth	1.7	2.2
Diarrhea	1.7	1.1
Abdominal Discomfort	1.5	1.9
Euphoria	1.5	0.4
Weakness	1.4	0.9
Confusion	1.3	0.5
Blurred Vision	1.3	1.3
Nightmares	1.2	1.7
Vertigo	1.2	0.8

The following adverse events have been reported with an incidence of 0.5 to 0.9%:

Central Nervous System:	Anorexia, ataxia, equilibrium loss, tremor, increased dreaming.
Cardiovascular:	Dyspnea, palpitations.
Gastrointestinal:	Vomiting.
Musculoskeletal:	Backache.
Special Senses:	Hyperhydrosis, burning eyes.

The following adverse events have been reported with an incidence of less than 0.5%: amnesia, hallucinations, horizontal nystagmus and paradoxical reactions including restlessness, overstimulation, and agitation.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Manifestations of acute overdosage of temazepam, as with other benzodiazepines, can be expected to reflect the increasing CNS effects of the drug and include somnolence, confusion and coma, with reduced or absent reflexes. With large overdoses, respiratory depression, hypotension, and finally coma will result. If the patient is conscious, vomiting should be induced mechanically or with emetics (e.g. syrup of ipecac 20 to 30 mL). Gastric lavage should be employed as soon as possible, utilizing concurrently a cuffed endotracheal tube if the patient is unconscious, in order to prevent aspiration and pulmonary complications. Maintenance of adequate pulmonary ventilation is essential and fluids should be administered intravenously to encourage diuresis. The use of pressor agents, such as norepinephrine bitartrate or metaraminol, intravenously may be necessary to combat hypotension but only if considered essential. The value of dialysis in emergency therapy for benzodiazepine overdosage has not been determined. If excitation occurs, barbiturates should not be used. It should be borne in mind that multiple agents may have been ingested.

The benzodiazepine antagonist, flumazenil, is a specific antidote in known or suspected benzodiazepine overdose. For conditions of use see flumazenil product monograph.

DOSAGE AND ADMINISTRATION

The lowest effective dose of TEMAZEPAM (temazepam) should be used. Treatment should usually not exceed 7 to 10 consecutive days.

Use of TEMAZEPAM for more than 2 to 3 consecutive weeks requires complete re-evaluation of the patient.

An appropriate hypnotic dose should produce the desired hypnotic effect while avoiding over-sedation and impairment of performance the next day.

ADULT DOSE

While the recommended usual adult dose is 15 mg before retiring, 7.5 mg may be sufficient for some patients and others may need 30 mg. In transient insomnia, a 7.5 mg dose may be sufficient to improve sleep latency.

ELDERLY AND DEBILITATED PATIENTS

The initial dose should not exceed 15 mg before retiring (see PRECAUTIONS).

TEMAZEPAM is intended only for short-term use and therefore, should not be prescribed in quantities exceeding those required for that cycle of administration. Prescription should not be renewed without further assessment of the patient's needs.

CHILDREN

TEMAZEPAM is not indicated in children under 18 years of age.

PHARMACEUTICAL INFORMATION

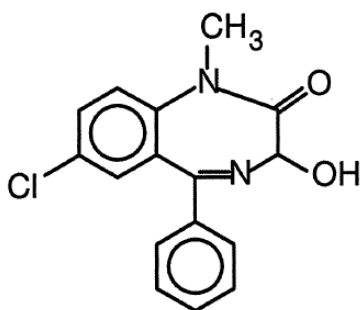
DRUG SUBSTANCE

Common Name: Temazepam

Chemical Names:

- 1) 2*H*-1,4-Benzodiazepine-2-one,7-chloro-1,3-dihydro-3-hydroxy-1-methyl-5-phenyl-;
- 2) 7-Chloro-1,3-dihydro-3-hydroxy-1-methyl-5-phenyl-2*H*-1,4-benzodiazepine-2-one.

Structural Formula:



Molecular Formula: C₁₆H₁₃ClN₂O₂

Molecular Weight: 300.74

Description: A white or almost white odourless, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in chloroform. Melting point 156°C to 162°C.

COMPOSITION

TEMAZEPAM (temazepam) Capsules contain the following non-medicinal ingredients (in alphabetical order): ammonium hydroxide, croscarmellose sodium, D&C Red No. 28, FD&C Blue No. 1, FD&C Red No. 40 (15 mg and 30 mg capsules only), gelatin, isopropyl alcohol, lactose anhydrous, magnesium stearate, microcrystalline cellulose, N-butyl alcohol, pharmaceutical glaze, propylene glycol, red iron oxide T (15 mg capsules only), simethicone, sodium lauryl sulfate and titanium dioxide.

STABILITY AND STORAGE RECOMMENDATIONS

Store at room temperature (15°C to 25°C) in well-closed, light-resistant containers.

Keep out of reach and sight of children.

AVAILABILITY OF DOSAGE FORMS

TEMAZEPAM (temazepam) is available in the following dosage forms:

Temazepam 15 mg

Capsules containing 15 mg of temazepam (pink opaque body, maroon opaque cap, hard gelatin capsule, imprinted TM 15, with white powder fill) are available in bottles of 100.

Temazepam 30 mg

Capsules containing 30 mg of temazepam (light blue opaque body, maroon opaque cap, hard gelatin capsule, imprinted TM 30, with white powder fill) are available in bottles of 100.

INFORMATION FOR THE PATIENT

FACTS ON TEMAZEPAM Temazepam Capsules USP

INTRODUCTION

TEMAZEPAM (temazepam) is intended to help you sleep. It is one of several benzodiazepine 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 longer you use the medication, the less effective it may become,**
- **you may become dependent on the medication,**
- **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 temazepam in particular.

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

SAFE USE OF TEMAZEPAM SLEEPING PILLS

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

DO NOT TAKE TEMAZEPAM for more than 7 to 10 days without first consulting your doctor.

DO NOT TAKE TEMAZEPAM 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 TEMAZEPAM 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 TEMAZEPAM.

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.

If you develop any unusual disturbing thoughts or behaviour while using TEMAZEPAM 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 TEMAZEPAM.

EFFECTIVENESS OF BENZODIAZEPINE SLEEPING PILLS

Benzodiazepine sleeping pills are effective medications and are 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 risk and benefits of prolonged use should be discussed with your doctor.

SIDE EFFECTS

Common Side Effects: Benzodiazepine sleeping pills 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 TEMAZEPAM. Do not use benzodiazepine sleeping pills 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. For this reason, it is important that you use the lowest effective dose.

Benzodiazepines 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: All benzodiazepine sleeping pills can 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".

Tolerance/Withdrawal Symptoms: After nightly use for more than a few weeks these drugs may lose some of their effectiveness. You may also develop a degree of dependence.

For benzodiazepine sleeping pills that the body eliminates quickly, there may be a deficiency of the drug in the body at some point between each night's use. This "withdrawal" can lead to (1) being awake during the last third of the night, and (2) increased daytime anxiety or nervousness.

Withdrawal effects can occur when patients stop taking benzodiazepine sleeping pills. The effects may occur following use for only a week or two but may be more common and severe after long periods of continuous use. One type of withdrawal symptom is known as "rebound insomnia", i.e., on the first few nights after stopping the medication, insomnia may be worse than before the sleeping pill was given.

Other withdrawal symptoms 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.

Dependence/Abuse: All benzodiazepine 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, either at the prescribed dose or at higher doses - 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 behaviour changes may occur when you use benzodiazepine 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 such as confusion, strange behaviour, restlessness, illusions, hallucinations, feeling like you are not yourself, and worsening depression, including 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 to your doctor.

EFFECT ON PREGNANCY

Certain benzodiazepine sleeping pills have been linked to birth defects when taken during the early months of pregnancy. In addition, benzodiazepine sleeping pills taken during the last weeks of pregnancy have been known to sedate the baby. Therefore, **AVOID USING THIS MEDICATION DURING PREGNANCY.**

PHARMACOLOGY

ANIMAL PHARMACOLOGY

In animals, temazepam produces sedative and muscle relaxant effects. At higher doses it has some cardiovascular depressant effects. In unanesthetized rabbits and dogs, temazepam caused slight but significant decreases in blood pressure at oral doses from 5 to 20 mg/kg.

Temazepam decreases spontaneous activity at doses of 2.5 and 5 mg/kg p.o. in the mouse, 20 mg/kg p.o. in the rat and at 10 mg/kg p.o. in the dog. It produces ataxia in the mouse and rat at 10 mg/kg p.o. and in the dog at 20 mg/kg p.o. Loss of righting reflex occurs in the mouse and rat at 40 mg/kg p.o. and muscle tone is decreased in the mouse at 10 to 40 mg/kg p.o. and in the rat and dog at 20 mg/kg p.o. Ptosis, myosis and piloerection occur in the mouse at 2.5 to 5 mg/kg p.o., in the rat at 10 to 20 mg/kg p.o., and in the dog bradycardia occurs at 20 to 40 mg/kg and photophobia at 80 mg/kg p.o.

Temazepam potentiates the sleep-enhancing effects of hexobarbitone, induces sleep in cebus monkeys at the minimum effective dose of 3.75 mg/kg p.o. and blocks the lingomandibular reflex in cats at the dose of 0.1 to 1.0 mg/kg i.v. Temazepam also blocks pentylenetetrazol-induced convulsions in mice at the dose of 0.23 mg/kg p.o.

PHARMACOKINETICS

Metabolism and excretion of temazepam in toxicology species (mouse, rat and dog) varied considerably from the pattern in man but the biotransformation pathways in humans also occur in all of the animals studied thus far. In mice, the major metabolites were N-desmethyltemazepam and its conjugates. In the rat, temazepam and the N-demethylated compound were present in equal proportions, largely unconjugated, but more than 50% was present as unidentified metabolites. In the dog, conjugated temazepam was the major metabolite, followed by free and conjugated N-desmethyltemazepam in equal proportions. In all species studied, man showed the highest blood levels, the smallest distribution volume and the greatest proportion of urinary elimination.

TOXICOLOGY

In the acute toxicity studies the following LD₅₀ for temazepam were determined:

Acute LD₅₀ (mg/kg) of Temazepam			
Species	Sex	Routes	LD₅₀ mg/kg
Mouse Mouse	M & F M	Oral Oral	1963 (1813-2126) 980 (860-1117)
Mouse Mouse	M & F M	i.p. i.p.	1050 (967-1140) 485 (411-572)
Rat Rat	M & F M	Oral Oral	1823 (1639-2027) 2800 (2059-3808)
Rat Rat	M & F M	i.p. i.p.	617 (551-690) 670 (626-717)
Rabbit	M & F	Oral	≥2400
Dog	M & F	Oral	≥1600

Overt sedation was prominent in all acute tests and ataxia and decreased locomotion were observed in some tests.

Subacute toxicity experiments lasting from 6 to 13 weeks were conducted in rats (9-250 mg/kg/day p.o.) and dogs (80-200 mg/kg/day p.o.). In the rat changes in hepatic function were seen at the doses over 100 mg/kg/day.

In subacute studies in dogs treatment-related symptoms included decreased locomotion, sedation, abdominal distension and weight loss. Sporadic hyperexcitability was seen in some animals. Chronic toxicity studies of 6 to 12 months were performed in rats (10-160 mg/kg/day p.o.) and dogs (5 to 120 mg/kg/day p.o.). In the rat the major finding was a liver weight increase at high doses and minimal hepatic lipidosis at the mid and high doses. Dogs at the higher doses employed exhibited slight lethargy.

Two series of 18 month studies were performed in mice at doses from 11 to 158 mg/kg/day. In one study there was a 4% increase over controls in hepatocellular adenomas in female mice. This incidence is within that found in control groups for the species studies.

REPRODUCTION AND TERATOLOGY STUDIES

Rats (25 to 840 mg/kg/day) and rabbits (5 to 60 mg/kg/day) were utilized to assess potential reproductive and teratologic effects. Two segment II type studies in rats provided evidence of the possible increased incidence of fetal resorptions, at doses of 30 to 120 mg/kg. In perinatal and postnatal studies in rats at doses of 60 and 120 mg/kg/day resulted in increasing nursing mortality. There were minimal untoward effects on the newborn survival rate. Two segment II type studies in rabbits produced no evidence of potential teratologic effects.

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