PRODUCT MONOGRAPH

NITRAZEPAM - 5
NITRAZEPAM - 10

Nitrazepam Tablets BP

5 and 10 mg

Hypnotic and Anticonvulsant

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Date of Preparation
June 23, 2004

Control # 092305

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THERAPEUTIC CLASSIFICATION

Hypnotic and Anticonvulsant

ACTIONS AND CLINICAL PHARMACOLOGY

Nitrazepam is a benzodiazepine with hypnotic and anticonvulsant properties.

In sleep laboratory studies nitrazepam decreased sleep latency, increased total sleep time and decreased awake time. There is delay in the onset, and decrease in the duration of REM sleep. Nitrazepam is reported to significantly decrease stage 1, 3 and 4 sleep and to increase stage 2. Following discontinuation of the drug, REM sleep rebound has been reported in some studies.

Nitrazepam has been shown to raise the seizure threshold.

GENERAL BENZODIAZEPINE CLINICAL PHARMACOLOGY

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 daytime anxiety (see WARNINGS).

Nitrazepam has an intermediate half-life.

PHARMACOKINETICS

Nitrazepam is rapidly absorbed from the gastrointestinal tract. Bioavailability after an oral dose averages about 80%. Peak blood concentrations after oral administration are observed in approximately 3 hours.

Following the administration of single oral doses of 5 or 10 mg nitrazepam to healthy volunteers, mean peak plasma concentrations ranged between 23-66 ng/mL and 55-107 ng/mL, respectively. In elderly patients suffering from various debilitating diseases, a mean peak plasma concentration of 22 ng/mL was observed after a single dose of 5 mg nitrazepam. Steady state plasma concentrations following administration of 5 mg nitrazepam once daily were reached after approximately 4 days. Steady state plasma concentrations of nitrazepam were approximately 40 ng/mL.

Nitrazepam is a lipophilic drug and crosses the membrane barriers of the body readily. The concentrations in cerebrospinal fluid, about 10% of the total plasma level, are similar to the protein free fraction of plasma. Following oral administration, mean volumes of distribution were greater in elderly patients than in young volunteers (4.8 ± 1.7 vs 2.4 ± 0.8 L/kg, respectively).

Total clearance was not significantly different in the two groups (78 ± 25 and 68 ± 33 mL/min, respectively).

Nitrazepam has no clinically active metabolites. The drug is excreted in human urine mainly as conjugated and non-conjugated aminonitrazepam and aceta-midonitrazepam. When given orally, 65 to 71% of the dose eventually appears in the urine and 14 to 20% in the feces. Only about 1% of the administered dose is excreted in the urine as unchanged nitrazepam. The major pathway involves hepatic nitroreduction.

The half-life of nitrazepam in healthy young volunteers is approximately 30 hours (range 18 to 57 hours). Elderly, ill patients showed a prolonged half-life of approximately 40 hours. Due to its slow elimination, nitrazepam accumulates when taken every night.

Approximately 87% of unchanged nitrazepam is bound to plasma proteins. In patients with liver cirrhosis, protein binding was significantly less than in healthy subjects (19% vs 14% unbound). In patients with mild to moderate renal insufficiency, protein binding was somewhat less than in healthy volunteers (16.8% vs 15.0% unbound).

Nitrazepam crosses the placental barrier and is excreted in maternal milk. Milk nitrazepam concentrations increased significantly from the first (30 nmol/L) to the fifth morning (48 nmol/L) in nursing mothers receiving 5 mg nitrazepam at night. The milk to plasma ratio of nitrazepam was 0.27 after 7 hours and did not vary from day 1 to day 5.

COMPARATIVE BIOAVAILABILITY

A standard, randomized, two-way crossover study was conducted in 19 healthy, adult, male volunteers to evaluate the relative bioavailability of single oral doses of NITRAZEPAM – 10 mg

Tablets and Mogadon® 10 mg Tablets. The mean pharmacokinetic parameters of these subjects are summarized in the following table.

Fasting Study: Summary Table of the Comparative Bioavailability Data Nitrazepam (Dose: 1x10 mg) From Measured Data			
	Geometric Mean Arithmetic Mean (CV%)		
Parameter	NITRAZEPAM – 10 10 mg Tablets	MOGADON®† 10 mg Tablets	Ratio of Geometric Means (%)**
AUC_{0-72} (ng·h/mL)	2425.37 2496.91 (30)	2447.76 2532.93 (33)	99.1%
AUC_{1} (ng·h/mL)	3053.03 3133.21 (27)	3082.57 3181.37 (31)	99.0%
C_{MAX} (ng/mL)	104.12 108.98 (33)	104.83 108.88 (33)	99.3%
T_{MAX} * (h)	1.90 (51)	1.69 (51)	-
$T_{1/2}$ * (h)	32.15 (10)	32.18 (12)	-

* Arithmetic means (CV%); ** Based on the least squares estimate;
† Mogadon® is marketed by ICN Canada Limited and was purchased in Canada.

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.

NITRAZEPAM 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 NITRAZEPAM 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 NITRAZEPAM 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.

NITRAZEPAM is also useful for the management of myoclonic seizures.

CONTRAINDICATIONS

NITRAZEPAM is contraindicated in patients with known hypersensitivity to benzodiazepines, any component to its formulation, and in those with severe impairment of respiratory function, e.g., significant sleep apnea syndrome.

NITRAZEPAM is contraindicated in patients who have myasthenia gravis or severe hepatic insufficiency. NITRAZEPAM is contraindicated in children when used as a hypnotic.

WARNINGS

GENERAL

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

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.

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

PREGNANCY

The use of nitrazepam 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 benzodiazepine hypnotic has resulted in neonatal CNS depression due to transplacental distribution. If nitrazepam is prescribed to women 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 might be pregnant.

MEMORY DISTURBANCE

Anterograde amnesia of varying severity has been reported following therapeutic doses of benzodiazepines. The event is rare with nitrazepam. 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 benzodiazepines, 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 nitrazepam 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 nitrazepam, 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 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 short half-life benzodiazepines although the syndrome can apply on occasion to drugs with longer elimination half-lives as well. Nitrazepam has an intermediate half-life.

DEPRESSION

Caution should be exercised if nitrazepam 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.

PRECAUTIONS

DRUG INTERACTIONS

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

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

TOLERANCE

Some tolerance to the hypnotic effects of benzodiazepines may develop after repeated use.

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, insomnia, headache, extreme anxiety, tension, restlessness, confusion and irritability) have occurred following abrupt discontinuation of benzodiazepines, and may follow the discontinuation of nitrazepam. In severe cases, the following symptoms may occur: derealization, depersonalization, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations and epileptic seizures. The 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 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. Caution must be exercised if it is at all necessary to administer nitrazepam to these individuals.

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. Moreover, 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.

REBOUND INSOMNIA

A transient syndrome whereby the symptoms that led to treatment with a benzodiazepine or benzodiazepine-like agent recur in an enhanced from, may occur on withdrawal of hypnotic treatment. It may be accompanied by other reactions including mood changes, anxiety and restlessness.

PATIENTS WITH SPECIFIC CONDITIONS

Nitrazepam should be given with caution to patients with impaired hepatic or renal function, and is contraindicated in patients with severe impairment of hepatic or respiratory function. Respiratory depression has been reported in patients with compromised respiratory function. A lower dose is also recommended for patients with chronic respiratory insufficiency due to the risk of respiratory depression. Benzodiazepines are not recommended for the primary treatment of psychotic illness.

PATIENTS REQUIRING MENTAL ALERTNESS

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

BRONCHIAL HYPERSECRETION, EXCESSIVE SALIVATION

In infants and young children, as well as elderly, bed-ridden patients, bronchial hypersecretion and excessive salivation leading to aspiration/pneumonia may occur on rare occasions.

USE IN PREGNANCY

Nitrazepam is not recommended for use during 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.

USE IN NORSING MOTHERS

Since nitrazepam is excreted in maternal milk, nursing should not be undertaken while the patient is taking nitrazepam.

USE IN CHILDREN

The safety and effectiveness of nitrazepam as a hypnotic in children below the age of 18 have not been established (See CONTRAINDICATIONS Section).

USE IN THE 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 events/falls. Therefore, the lowest possible dose should be used in these subjects.

ADVERSE REACTIONS

The most common adverse reactions are fatigue, dizziness, lightheadedness, drowsiness, lethargy, mental confusion, staggering, ataxia and falling. These phenomena occur predominantly at the start of therapy and usually disappear with repeated administration.

Depressed dreaming and nightmares have also been reported.

Sedative effects can often be decreased by a reduction in dosage. Children, the elderly and/or debilitated patients are more susceptible to sedative effects and paradoxical reactions. Therefore, these patients should be carefully screened before they are given hypnotics and the lowest effective dose should be used. Paradoxical reactions such as agitation, hyperactivity, excitement, hallucinations, increased muscle spasticity, aggressiveness, irritability, rages, psychoses and violent behaviour have been reported in rare instances when using drugs that act as the benzodiazepine receptors. Should these occur, the drug should be discontinued.

Hangover, disorientation, severe sedation, hypotension, signs and symptoms of withdrawal including delirium tremens, and cutaneous reactions have been reported. Headache, heartburn, upset stomach, diarrhea, constipation, nausea, vomiting, weakness, faintness, palpitations, blurred vision, dyspnea, nervousness, apprehension, depression, numbed emotions, changes in libido, inappropriate behaviour, altered hepatic function tests and, in rare instances, leucopenia and granulocytopenia have been reported with this drug or other drugs of this class.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

SYMPTOMS

The cardinal manifestations are drowsiness, confusion, reduced reflexes, increasing sedation, and coma. Effects on respiration, pulse and blood pressure are noticed with large overdoses. Patients exhibit some jitteriness and over stimulation usually when the effects of the drug begin to wear off.

TREATMENT

In the management of overdose with any medicinal product, it should be borne in mind that multiple agents may have been taken. Following overdose with nitrazepam vomiting should be induced (within one hour) if the patient is conscious or gastric lavage undertaken with the airway

protected if the patient is unconscious. If there is no advantage in emptying the stomach, activated charcoal should be given to reduce absorption. If respiratory depression and/or coma are observed, the presence of other central nervous system depressants should be suspected. Respirations, pulse and blood pressure should be monitored. General supportive measures aimed at maintaining cardiopulmonary function should be instituted and administration of intravenous fluids started. Hypotension and CNS depression are managed by the usual means. Dialysis is usually of little value.

USE OF REVERSAL AGENT

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

The use of 'Anexate' **is not** recommended in epileptic patients who have been treated with nitrazepam (or any other benzodiazepine). The reversal of the benzodiazepine effect could induce convulsions in such patients.

DOSAGE AND ADMINISTRATION

The lowest effective dose of NITRAZEPAM should be used. Treatment with NITRAZEPAM should be as short as possible, and should usually not exceed 7-10 consecutive days. Use for more than 2-3 consecutive weeks requires complete re-evaluation of the patient. NITRAZEPAM should be withdrawn for a treatment-free period at regular intervals to ascertain whether the therapy needs to be continued.

Dosage of NITRAZEPAM should be individualized for maximal beneficial effect.

NITRAZEPAM tablets may be swallowed whole, chewed or dissolved in liquid.

INSOMNIA

Adults:

The usual adult dose is 5 or 10 mg before retiring.

Elderly and/or Debilitated Patients:

It is recommended that in these patients therapy be initiated with 2.5 mg until individual responses are determined. Doses higher than 5 mg are usually not recommended in the elderly.

MYOCLONIC SEIZURES

Children:

The usual dose for children (up to 30 kg of body weight) is between 0.3 and 1.0 mg/kg/day given in three divided doses. Treatment should be initiated with a lower dose than the usual recommended dosage range in order to determine tolerance and response. If a dose within the recommended dosage range does not control the condition, a higher dosage may be gradually attempted. Higher doses may cause excessive drowsiness, and may cause bronchial hypersecretion in infants with epilepsy. The use of NITRAZEPAM in infants with epilepsy must be examined before treatment is started in order to determine whether the upper airways are clear. Whenever possible the daily dosage should be divided into three equal doses. If doses are not equally divided, the larger dose should be given before retiring. In some patients tolerance develops to the effects of nitrazepam.

The use of multiple anticonvulsants may result in an increase of central nervous system depressant adverse effects. This should be borne in mind whenever NITRAZEPAM is added to an already existing anticonvulsant regimen.

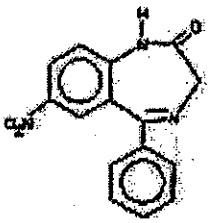
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Common Name: Nitrazepam

Chemical Name: 1,3-dihydro-7-nitro-5-phenyl-2H-1,4-benzodiazepin-2-one

Structural Formula:



Molecular Formula: $C_{15}H_{11}N_3O_3$

Molecular Weight: 281.3

Description: Nitrazepam is a yellow, crystalline powder. It is practically insoluble in water, slightly soluble in ethanol (96%) and in ether; sparingly soluble in chloroform.

COMPOSITION

Each NITRAZEPAM tablet contains either 5 or 10 mg of nitrazepam, lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate.

STABILITY AND STORAGE RECOMMENDATIONS

Store at room temperature (15 - 30°C). Protect from light.

AVAILABILITY OF DOSAGE FORMS

NITRAZEPAM – 5 (nitrazepam) 5 mg tablets are round, white, biplane, bevelled edged tablets, engraved 'NIT' over '5' on one side, plain on the other side.

NITRAZEPAM – 10 (nitrazepam) 10 mg tablets are round, white, biplane, bevelled edged tablets, scored and engraved 'NIT' over '10' on one side, plain on the other side.

NITRAZEPAM Tablets BP, 5 and 10 mg are available in bottles of 100 and 500 tablets, unit dose packages of 100 tablets.

INFORMATION FOR THE PATIENT

Facts On NITRAZEPAM (nitrazepam) Tablets

Introduction

NITRAZEPAM 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 NITRAZEPAM in particular.

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

Safe Use Of NITRAZEPAM Sleeping Pills

- NITRAZEPAM is a prescription medication, intended to help you sleep. Follow your doctor's advice about how to take NITRAZEPAM, when to take it, and how long to take it. DO NOT TAKE NITRAZEPAM if it is not prescribed for you.
- DO NOT TAKE NITRAZEPAM for more than 7-10 days without first consulting your doctor.
- DO NOT TAKE NITRAZEPAM 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 NITRAZEPAM 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 NITRAZEPAM.
- 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 NITRAZEPAM, 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 NITRAZEPAM.

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 risks 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 NITRAZEPAM. 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.

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 benzodiazepines may lose some of their effectiveness. You may also develop a degree of dependence.

"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, similar in character to those noted with barbiturates and alcohol (convulsions, tremor, abdominal and muscle cramps, vomiting, sweating, dysphoria, perceptual disturbances, insomnia, headache, extreme anxiety, tension, restlessness, confusion and irritability) have occurred following abrupt discontinuation of benzodiazepines, and may follow the discontinuation of NITRAZEPAM. In severe cases, the following symptoms may occur: sense of detachment from one's surroundings, unreal feeling with a sensation that the extremities have

changed size, abnormal sensitivity to sound, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations and epileptic seizures. The more severe symptoms are usually associated with higher dosages and longer usage.

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.

Excessive Salivation:

On rare occasions in infants and young children, as well as elderly, bed-ridden patients, there may be excessive secretion of saliva and fluid in the lungs which may lead to chest infections.

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 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

In animal tests, nitrazepam produces sedative, hypnotic, taming, muscle relaxant and anticonvulsant effects. It selectively suppresses metrazole-induced seizures. After I.V. administration of doses of 1 to 8 mg/kg to dogs and cats, nitrazepam did not significantly modify the systolic or diastolic blood pressure. However, in both species, there was a significant reduction in heart rate, particularly evident at the highest dose. Blood pressure response to norepinephrine and serotonin was inhibited while the response to histamine was somewhat prolonged. Nitrazepam had a depressant effect on both the spontaneous and the activated EEG after relatively high intravenous doses, i.e., 1 to 10 mg. The same doses produced a marked reduction in the response to hypothalamic as well as reticular activating system (RAS) stimulations, whereas there was an increase in the threshold upon stimulation of the limbic system.

TOXICOLOGY

ACUTE TOXICITY

LD_{50}' s

Species	Route	Dose
Mouse	i.p. p.o.	275 mg/kg at 72 hours 1,800 mg/kg
Rat	i.p.	> 2,000 mg/kg at 24 hours 950 mg/kg at 10 days
	p.o.	> 2,000 mg/kg at 24 hours 1,000 mg/kg at 10 days

In dogs, doses of 1,200 mg/kg produced a three-day sleep and all animals survived.

SUBACUTE AND CHRONIC TOXICITY STUDIES

Oral doses of nitrazepam 10, 20, 80, 100, 240 and 320 mg/kg/day were administered to rats in a series of studies lasting from 6 to 78 weeks. At doses of 10, 20, 80 and 100 mg/kg/day no serious side effects were encountered, with the exception of an initial hyperexcitability followed by ataxia, and reduction in weight and food intake in the 100 mg/kg group. At doses of 240 and 320 mg/kg/day, a marked reduction in weight and food consumption was observed and most animals presented an unhealthy appearance. At these doses in males, testicular tubular degeneration and aspermiogenesis were produced. Deaths occurred caused either by diarrhea, convulsive seizures of brief duration or other acute toxic effects.

Oral doses of nitrazepam of 10, 20, 40 and 80 mg/kg/day were administered for 6 weeks to dogs. A significant sedative effect was observed at all dose levels. Histopathological examination revealed evidence of liver involvement in the dogs treated with 40 and 80 mg/kg/day (liver enlargement, cloudy swelling of liver). The six-month oral chronic toxicity study in the dog was performed with the same doses as the previous study. Lower doses were well tolerated. There

was loss of weight in the 40 and 80 mg/kg groups. Three dogs out of 6 in the 80 mg/kg group died during epileptiform seizures. There was increase weight of livers in the 40 and 80 mg/kg groups. Oral doses of 2.5, 10 and 40 mg/kg/day were administered to dogs in a study, lasting 55 to 56 weeks. At the highest dose elevated leucocyte counts, elevated sedimention rates, slight increase in liver weights, and edematous swelling of the forepaws were observed. No unusual histopathology was noted.

REPRODUCTIVE STUDIES

Reproductive studies in the rat, rabbit, mouse and dog, were performed using doses ranging from 2 to 100 mg/kg/day. At the 100 mg/kg/day dosage in the rat and rabbit, multiple skeletal defects and fetal resorption were produced. Nitrazepam may produce dose-related teratogenic effects in the rat. Changes in fertility and general reproductive performance may be related to its pharmacological action (sedative and hypnotic effect) in the animal species studied.

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