PRODUCT MONOGRAPH

MOGADON®

Nitrazepam Tablets BP
5 mg, 10 mg

Hypnotic and Anticonvulsant

AA PHARMA INC.
1156 Creditstone Road, Unit#1
Vaughan, Ontario
L4K 4N7

DATE OF REVISION:
August 12, 2021

Control No: 248565

Table of Contents

MOGADON®
Nitrazepam Tablets BP
5 mg, 10 mg

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Oral	Tablet / 5 mg, 10 mg	croscarmellose sodium, lactose monohydrate, magnesium stearate, and microcrystalline cellulose

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.

MOGADON (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 MOGADON 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 MOGADON 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.

MOGADON is also useful for the management of myoclonic seizures.

Geriatrics:

Long-term use of MOGADON should be avoided in elderly patients. Enhanced monitoring is recommended (see WARNINGS AND PRECAUTIONS, Falls and Fractures; DOSAGE AND ADMINISTRATION, Dosing considerations).

CONTRAINDICATIONS

MOGADON (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.

MOGADON is contraindicated in patients, who have myasthenia gravis or severe hepatic insufficiency.

MOGADON is contraindicated in children, when used as a hypnotic.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Addiction, Abuse and Misuse
The use of benzodiazepines, including MOGADON, can lead to abuse, misuse, addiction, physical dependence and withdrawal reactions. Abuse and misuse can result in overdose or death, especially when benzodiazepines are combined with other medicines, such as opioids, alcohol or illicit drugs.

- Assess each patient's risk prior to prescribing MOGADON
- Monitor all patients regularly for the development of these behaviours or conditions.
- MOGADON should be stored securely to avoid theft or misuse.

Withdrawal
Benzodiazepines, like MOGADON, can produce severe or life-threatening withdrawal symptoms.

- Avoid abrupt discontinuation or rapid dose reduction of MOGADON.
- Terminate treatment with MOGADON by gradually tapering the dosage schedule under close monitoring.

(see WARNINGS AND PRECAUTIONS, Dependence/Tolerance)

Risks from Concomitant use with Opioids
Concomitant use of MOGADON and opioids may result in profound sedation, respiratory depression, coma and death (see WARNINGS AND PRECAUTIONS, General, Concomitant use with opioids).

- Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are not possible.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

General

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. Such abnormalities 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.

Concomitant use with opioids: Concomitant use of benzodiazepines, including MOGADON, and opioids may result in profound sedation, respiratory depression, coma and death. Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are not possible (see SERIOUS WARNINGS AND PRECAUTIONS BOX, Risks from Concomitant use with Opioids; DRUG INTERACTIONS, Serious Drug Interactions).

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other central nervous system (CNS) depressant drugs with benzodiazepines.

If a decision is made to prescribe MOGADON concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of MOGADON than indicated, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking MOGADON, prescribe a lower initial dose of the opioid analgesic and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation (see OVERDOSAGE).

Advise both patients and caregivers about the risks of respiratory depression and sedation when MOGADON is used with opioids.

Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the opioid have been determined.

Complex Sleep-related Behaviours

Complex sleep-related behaviours, such as “sleep-driving” (i.e., driving while not fully awake after ingestion of a sedative-hypnotic, with amnesia for the event), have been reported in patients who have taken nitrazepam. Other potentially dangerous behaviours have been reported in patients who got out of bed after taking a sedative-hypnotic and were not fully awake, including preparing and eating food, making phone calls, leaving the house, etc. As with “sleep-driving”, patients usually do not remember these events. The use of alcohol and other CNS-depressants with nitrazepam appears to increase the risk of such behaviours, as does the use of nitrazepam at doses exceeding the maximum recommended dose. Nitrazepam is not to be taken with alcohol. Caution is needed with concomitant use of other CNS depressant drugs. Due to the risk to the patient and the community, discontinuation of nitrazepam should be strongly considered for patients who report any such sleep-related behaviours.

Dependence/Tolerance

Use of benzodiazepines, such as MOGADON, can lead to abuse, misuse, addiction, physical dependence (including tolerance) and withdrawal reactions. Abuse and misuse can result in overdose or death, especially when benzodiazepines are combined with other medicines, such as opioids, alcohol, or illicit drugs.

The risk of dependence increases with higher doses and longer term use but can occur with short-term use at recommended therapeutic doses. The risk of dependence is greater in patients with a history of psychiatric disorders and/or substance (including alcohol) use disorder.

- Discuss the risks of treatment with MOGADON with the patient, considering alternative (including non-drug) treatment options.
- Carefully evaluate each patient's risk of abuse, misuse and addiction, considering their medical condition and concomitant drug use, prior to prescribing MOGADON. In individuals prone to substance use disorder, MOGADON should only be administered if deemed medically necessary, employing extreme caution and close supervision.
- MOGADON should always be prescribed at the lowest effective dose for the shortest duration possible.
- All patients receiving benzodiazepines should be routinely monitored for signs and symptoms of misuse and abuse. If a substance use disorder is suspected, evaluate the patient and refer them for substance abuse treatment, as appropriate.

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

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.

Withdrawal: Benzodiazepines, such as MOGADON, can produce withdrawal signs and symptoms, ranging from mild to severe and even life threatening, following abrupt discontinuation or rapid dose reduction. Other factors that may precipitate withdrawal are switching from a long-acting to a short-acting benzodiazepine, decreasing blood levels of the drug or administration of an antagonist. The risk of withdrawal is higher with higher dosages and/or prolonged use, but can occur with short-term use at recommended therapeutic doses. The onset of withdrawal signs and symptoms can range from hours to weeks following drug cessation and occur even with tapered dosage. Some symptoms can persist for months. Since symptoms are often similar to those for which the patient is being treated, it may be difficult to distinguish from a relapse of the patient's condition.

Severe or life-threatening signs and symptoms of withdrawal include catatonia, delirium tremens, depression, dissociative effects (e.g. hallucinations), mania, psychosis, seizures (including status epilepticus) and suicidal ideation and behaviour.

Other withdrawal signs and symptoms include abdominal cramps, cognitive impairment, diarrhea, dysphoria, extreme anxiety or panic attacks, headache, hypersensitivity to light, noise and physical contact, insomnia, irritability, muscle pain or stiffness, paresthesia, restlessness, sweating, tension, tremors and vomiting. There is also a possibility of rebound anxiety or rebound insomnia.

- Abrupt discontinuation should be avoided and treatment - even if only of short duration - should be terminated by gradually tapering the dosage schedule under close monitoring.
- Tapering should be tailored to the specific patient. Special attention should be given to patients with a history of seizure.
- If a patient experiences withdrawal symptoms, consider postponing the taper or raising the benzodiazepine to the previous dosage prior to proceeding with a gradual taper.
- Inform patients of risk of discontinuing abruptly, reducing dosage rapidly or switching medications.
- Stress the importance of consulting with their health care professional in order to discontinue safely.
- Patients experiencing withdrawal symptoms should seek immediate medical attention.

(see SERIOUS WARNINGS AND PRECAUTIONS BOX, Addiction, Abuse and Misuse, Withdrawal; DOSAGE AND ADMINISTRATION, Dosing Considerations).

Driving and Operating Machinery

Due to the CNS depressant effects of nitrazepam, 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.

Falls and Fractures

There have been reports of falls and fractures among benzodiazepine users due to adverse reactions such as sedation, dizziness and ataxia. The risk is increased in those taking concomitant sedatives (including alcoholic beverages), the elderly or debilitated patients.

Hepatic/Biliary/Pancreatic

Nitrazepam should be given with caution to patients with impaired hepatic function, and is contraindicated in patients with severe impairment of hepatic function. (see CONTRAINDICATIONS)

Hypersensitivity

Severe Anaphylactic and Anaphylactoid Reactions: Rare cases of angioedema involving the tongue, glottis or larynx have been reported in patients after taking the first or subsequent doses

of sedative-hypnotics, including nitrazepam. Some patients have had additional symptoms such as dyspnea, throat closing or nausea and vomiting that suggest anaphylaxis. Some patients have required medical therapy in the emergency department. If angioedema involves the throat, glottis or larynx, airway obstruction may occur and be fatal. Patients who develop angioedema after treatment with nitrazepam should not be rechallenged with the drug. (see CONTRAINDICATIONS)

Neurologic

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 cognitive impairment.

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 to resume full activity.

Psychiatric

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 benzodiazepines. Psychotic behavioural changes, reported with benzodiazepines, include abnormal 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. (see SERIOUS WARNINGS AND PRECAUTIONS BOX, Withdrawal)

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

Anxiety/Restlessness: An increase in daytime anxiety and/or restlessness has been observed during treatment with short half-life benzodiazepines. However, 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.

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.

Renal

Nitrazepam should be given with caution to patients with impaired renal function.

Respiratory

Nitrazepam is contraindicated in patients with severe impairment of 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 illnesses. (see CONTRAINDICATIONS)

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.

Special Populations

Pregnant Women: Nitrazepam should not be used during pregnancy, as benzodiazepines may cause foetal damage. Several studies have suggested an increased risk of congenital malformations associated with the use of the benzodiazepines during pregnancy (see WARNINGS AND PRECAUTIONS; see TOXICOLOGY).

During the last weeks of pregnancy, ingestion of therapeutic doses of benzodiazepine has resulted in neonatal CNS depression due to transplacental distribution. Infants of mothers who ingested benzodiazepines for several weeks or more preceding delivery have been reported to have withdrawal symptoms during the postnatal period. Symptoms such as hypoactivity, hypotonia, hypothermia, respiratory depression, apnea, feeding problems, and impaired metabolic response to cold stress have been reported in neonates born of mothers who have received benzodiazepines during the late phase of pregnancy or at delivery. Also, neonatal flaccidity has been reported in an infant born to a mother who had been receiving benzodiazepines.

Since nitrazepam is also a benzodiazepine derivative, its administration is rarely justified in women of child-bearing potential. If nitrazepam is prescribed to a woman of childbearing potential, she should be warned of the potential risk to a foetus 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.

Breast-Feeding Women: Since nitrazepam is excreted in maternal milk, breast-feeding should

not be undertaken, while the patient is taking nitrazepam.

Sedation and inability to suckle have occurred in neonates of lactating mothers taking benzodiazepines. Infants of lactating mothers should be observed for pharmacological effects (including sedation and irritability).

Pediatrics: The safety and effectiveness of nitrazepam, as a hypnotic, in children below the age of 18 have not been established (See CONTRAINDICATIONS; see TOXICOLOGY).

Geriatrics: As elderly patients are especially susceptible to dose-related adverse effects, the lowest possible dose should be used in these subjects. Long-term use of MOGADON should be avoided in elderly or debilitated patients who may be more sensitive to benzodiazepines. There is an increased risk of cognitive impairment, delirium, falls, fractures, hospitalizations and motor vehicle accidents in these users. Enhanced monitoring is recommended in this population.

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 at 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.

Post-Market Adverse Reactions

Injury, Poisoning and Procedural Complications: There have been reports of falls and fractures in benzodiazepine users due to adverse reactions such as sedation, dizziness and ataxia. The risk is increased in those taking concomitant sedatives (including alcoholic beverages), the elderly and debilitated patients.

Dependence/Withdrawal: Development of physical dependence and withdrawal following discontinuation of therapy has been observed with benzodiazepines such as MOGADON. Severe

and life-threatening symptoms have been reported. (see SERIOUS WARNINGS AND PRECAUTIONS BOX, Addiction, Abuse and Misuse; WARNINGS AND PRECAUTIONS, Dependence/Tolerance)

DRUG INTERACTIONS

Serious Drug Interactions

Concomitant use of MOGADON and opioids may result in profound sedation, respiratory depression, coma and death.

- Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are not possible.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

(see WARNINGS AND PRECAUTIONS, General, Risks from Concomitant use with Opioids)

Drug-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.

Opioids: Due to additive CNS depressant effect, the concomitant use of benzodiazepines, including MOGADON, and opioids increases the risk of profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations of concomitant use of benzodiazepines and opioids to the minimum required. Follow patients closely for respiratory depression and sedation (see SERIOUS WARNINGS AND PRECAUTIONS BOX, Risks from Concomitant use with Opioids; WARNINGS AND PRECAUTIONS, General, Concomitant use with opioids).

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

DOSAGE AND ADMINISTRATION

Dosing Considerations

- MOGADON should always be prescribed at the lowest effective dose for the shortest duration possible.

- Dosage of MOGADON should be individualized for maximal beneficial effect
- Treatment with MOGADON should be as short as possible, and 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.
- MOGADON should be withdrawn for a treatment-free period at regular intervals to ascertain whether the therapy needs to be continued.
- MOGADON can produce withdrawal signs and symptoms or rebound phenomena following abrupt discontinuation or rapid dose reduction (see SERIOUS WARNINGS AND PRECAUTIONS BOX, Withdrawal; WARNINGS AND PRECAUTIONS, Dependence/Tolerance). Abrupt discontinuation should be avoided and treatment - even if only of short duration - should be terminated by gradually tapering the dosage schedule under close monitoring.
- Tapering should be tailored to the specific patient. Special attention should be given to patients with a history of seizure.
- If a patient experiences withdrawal signs and symptoms, consider postponing the taper or raising the benzodiazepine to the previous dosage prior to proceeding with a gradual taper.
- Geriatric patients in particular may be more sensitive to benzodiazepines (see WARNINGS AND PRECAUTIONS, Falls and Fractures).
- Long-term use of MOGADON should be avoided in elderly patients. Enhanced monitoring is recommended.

Administration

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

Recommended Dose and Dosage Adjustment

Insomnia

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

Elderly and/or Debilitated Patients: The lowest possible effective dose should be prescribed for elderly 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

Pediatrics: 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 MOGADON 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 to the effects of nitrazepam may develop.

The use of multiple anticonvulsants may result in an increase of central nervous system

depressant adverse effects. This should be borne in mind whenever MOGADON is added to an already existing anticonvulsant regimen. (see CONTRAINDICATIONS)

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.

ACTION 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 AND PRECAUTIONS, Psychiatric, Anxiety/Restlessness).

Nitrazepam has an intermediate half-life.

Pharmacokinetics

Absorption: 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 to 66 ng/mL and 55 to 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.

Distribution: 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).

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).

Metabolism: 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.

Elimination: 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.

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 breast-feeding 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.

STORAGE AND STABILITY

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

Each MOGADON tablet contains either 5 or 10 mg of nitrazepam and the following non-medicinal ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate, and microcrystalline cellulose.

Availability of Dosage Forms

MOGADON 5 mg tablets are round, white, biplane, bevelled edged tablets, scored on one side, and engraved 'MOGADON' over '5' on the other side.

MOGADON 10 mg tablets are round, white, biplane, bevelled edged tablets, scored on one side, and engraved 'MOGADON' over '10' on the other side.

MOGADON Tablets, 5 and 10 mg are available in bottles of 100 tablets.

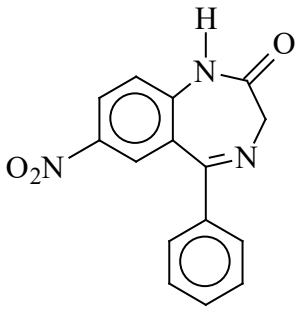
PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name:	Nitrazepam
Chemical Name:	1,3-dihydro-7-nitro-5-phenyl-2H-1,4-benzodiazepin-2-one
Molecular formula and molecular weight:	$C_{15}H_{11}N3_4O_3$ 281.3 g/mol

Structural Formula:



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

CLINICAL TRIALS

Comparative Bioavailability Studies

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 Mogadon® (additional formulation B) 10 mg Tablets and Mogadon® (original formulation A) 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			
Parameter	Geometric Mean Arithmetic Mean (CV%)		Ratio of Geometric Means (%)**
	MOGADON® (B) 10 mg Tablets	MOGADON® (A)† 10 mg Tablets	
AUC_{0-72} (ngXh/mL)	2425.37 2496.91 (30)	2447.76 2532.93 (33)	99.1%
AUC_I (ngXh/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)	--
$T_{½}$* (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.

DETAILED 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})

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 sedimentation 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.

Developmental Neurotoxicity

Nonclinical research has shown that administration of anesthetic and sedation drugs that block N-methyl-D-aspartate (NDMA) receptors and/or potentiate gamma-aminobutyric acid (GABA) activity can increase neuronal cell death in the brain and result in long-term deficits in cognition

and behaviour of juvenile animals when administered during the period of peak brain development. Based on comparisons across nonclinical species, the window of vulnerability of the brain to these effects is believed to correlate with human exposures in the third trimester of pregnancy through the first year of life, but may extend to approximately 3 years of age. While there is limited information of this effect with nitrazepam, similarities in pharmacology and mechanism of action suggest that a similar effect may occur. The relevance of these nonclinical findings to human use is unknown.

REFERENCES

Pharmacology

1) King DJ. Benzodiazepines, amnesia and sedation: theoretical and clinical issues and controversies. Hum Psychopharmacol 1992;7:79-87.
2) Kramer M, Schoen LS. Problems in the use of long-acting hypnotics in older patients. J Clin Psychiatry 1984; 45: 176-7.
3) Maczaj M. Pharmacological treatment of insomnia. Drugs 1993; 45: 44-55.
4) Matheson I, Lunde P, Bredesen J. Midazolam and nitrazepam in the maternity ward: milk concentrations and clinical effects. Br J Clin Pharmacol 1990; 30:787-93.
5) Muraoka M, Tada K, Nogami Y, et al. Residual effects of repeated administration of triazolam and nitrazepam in healthy volunteers. Neuropsychobiology 1992; 25:134-9.
6) Randall LO, Kappell B. Pharmacological activity of some benzodiazepines and their metabolites. In: Garattini S, Mussini E, Randall LO, ed., The benzodiazepines, Raven Press, New York, 1973: 27-51.
7) Diagnostic Classification Steering Committee. Thorpy MJ, Chairman. International classification of sleep disorders: diagnostic and coding manual. Rochester Minnesota, American Sleep Disorders Association, 1990.

Metabolism and Pharmacokinetics

8) Abernethy DR, Greenblatt DJ, Locniskar A, et al. Obesity effects on nitrazepam disposition. Br J Clin Pharmacol 1986; 22: 551-7.
9) Breimer DD. Clinical pharmacokinetics of hypnotics. Clin Pharmacokinetics 1977; 2:93-109.
10) Greenblatt DJ, Abernethy DR, Locniskar A, et al. Age, sex, and nitrazepam kinetics: relation to antipyrine disposition. Clin Pharm Ther 1985; 38:697-703.
11) Jochemsen R, Van Beusekom BR, Spoelstra P, et al. Effect of age and liver cirrhosis on the pharmacokinetics of nitrazepam. Br J Clin Pharmacol 1983; 15:295-302.
12) Kangas L, Kanto J, Erkkola R. Transfer of nitrazepam across the human placenta. Eur J Clin Pharmacol 1977; 12:355-7.
13) Kangas L, Breimer DD. Clinical pharmacokinetics of nitrazepam. Clin Pharmacokinet 1981; 6:346-66.
14) Oche H, Oberem U, Greenblatt D. Nitrazepam clearance unimpaired in patients with renal insufficiency. J Clin Psychopharmacol 1992; 12:183-5.
15) Ochs HR, Greenblatt DJ, Gugler R. Cimetidine impairs nitrazepam clearance. Clin Pharm Ther 1983; 34:227-30.
16) Rieder J, Wendt G. Pharmacokinetics and metabolism of the hypnotic nitrazepam. In: Garattini S, Mussini E, Randall LO, ed., The benzodiazepines, Raven Press, New York 1973: 99-127.

Clinical Hypnotic

17) Adam K, et al. Nitrazepam: lastingly effective but trouble on withdrawal. Brit Med J 1976; 1:1558-60.
18) Allnutt MF, O'Connor PJ. Comparison of the encephalographic, behavioral and subjective correlates of natural and drug-induced sleep at atypical hours. Aerospace

Med 1971; 42: 1006-10.
19) Baruzzi A, Michelucci R, Tassinari C. Benzodiazepines. Nitrazepam antiepileptic drugs, Third Edition, Raven Press: New York, NY-US 1989;785-804.
20) Bordeleau JM, et al. Hypnotic properties of nitrazepam. Dis Nerv Syst 1970; 31:318-325.
21) Cook PJ, Huggett A, Graham-Pole R, et al. Hypnotic accumulation and hangover in elderly inpatients: a controlled double-blind study of temazepam and nitrazepam. Br Med J 1983; 286: 100-2.
22) Haider I, Oswald I. Effects of amylobarbitone and nitrazepam on the electrodermogram and other features of sleep. Brit J Psychiat 1971; 118:519-22.
23) Kales A, et al. Rebound insomnia: a new clinical syndrome. Science 1978; 201: 1039-41.
24) Risberg AM, et al. Evaluation of the effect of fosazepam (a new benzodiazepine), nitrazepam and placebo on sleep patterns in normal subjects. Eur J Clin Pharmacol 1977; 12: 105-9.
25) Tada K, Nogami Y, Ishikawa K. The hypnotic and psychomotor effects of nitrazepram. Neuroscience 1991;17:401-8.

Clinical Anticonvulsant

26) Baldwin R, Kenny TJ, Segal J. The effectiveness of nitrazepam in a refractory epileptic population. Curr Ther Res 1969;11:413-7.
27) Jan JE, Riegl JA, Crichton JU, Dunn HG. Nitrazepam in the treatment of epilepsy in childhood. Can Med Assoc J 1971; 104: 571-5.
28) Markham CH. The treatment of myoclonic seizures of infancy and childhood with LA-1. Pediatrics 1964;34:511-8.
29) Snyder CH. Myoclonic epilepsy in children: short-term comparative study of two benzodiazepine derivatives in treatment. South Med J 1968;61:17-20.

OTHER

30) Product Monograph: Mogadon® (nitrazepam) Tablets. Valeant Canada Limited, Montreal, Quebec (Revised June 29, 2009).

PART III: CONSUMER INFORMATION

MOGADON®
Nitrazepam Tablets BP, 5 mg, 10 mg

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

ABOUT THIS MEDICATION

What the medication is used for:
MOGADON is intended to help you sleep if you have transient and short-term insomnia. Symptoms of insomnia include difficulty in falling asleep, and/or waking up often during the night or too early in the morning. Treatment with MOGADON should usually not go on for more than 7 to 10 days and should be restricted for insomnia where disturbed sleep results in impaired daytime functioning. MOGADON does not treat the underlying cause of your insomnia.

- MOGADON is also useful for the management of myoclonic seizures.

If you are 65 years or older, talk to your doctor before starting MOGADON. MOGADON may not be an effective treatment for you and you may be more sensitive to experiencing side effects.

What it does:
'Mogadon' is one of several benzodiazepine sleeping pills that have generally similar properties such as a calming effect.

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. (see "WARNINGS AND PRECAUTIONS")

When it should not be used:
Do not take MOGADON (nitrazepam) if you have:
- known allergy to nitrazepam or other benzodiazepines, or to any of the ingredients MOGADON contains (see "**What the nonmedicinal ingredients are**").
- severe lung or respiratory disease, including sleep apnea.
- myasthenia gravis, a chronic disease characterized by weakness of the skeletal muscles.
- a severe liver condition.

MOGADON is not to be used for insomnia in children under 18 years of age

What the medicinal ingredient is:
The medicinal ingredient in MOGADON is nitrazepam.

What the non-medicinal ingredients are:
MOGADON Tablets also contain the following non-medicinal ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate, and microcrystalline cellulose.

What dosage forms it comes in:
MOGADON is available in tablets of 5 mg and 10 mg strengths for oral administration.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Addiction, Abuse and Misuse: Even if you take MOGADON exactly as you were told to, you are at risk for abuse, misuse, addiction, physical dependence and withdrawal. Abuse and misuse can result in overdose or death, especially if you take MOGADON with:
- **opioids**
- **alcohol or**
- **illicit drugs**

Your doctor should:
- **talk to you about the risks of treatment with MOGADON as well as other treatment (including non-drug) options**
- **assess your risk for these behaviours before prescribing MOGADON**
- **monitor you while you are taking MOGADON for the signs and symptoms of misuse and abuse. If you feel like you are craving MOGADON, or not using it as directed, talk to your doctor right away.**

Store MOGADON in a secure place to avoid theft or misuse.

Withdrawal: If you suddenly stop taking MOGADON, lower your dose too fast, or switch to another medication, you can experience severe or life-threatening withdrawal symptoms (see Withdrawal section below)

- **Always contact your doctor before stopping, or lowering your dose of MOGADON or changing your medicine.**

MOGADON with Opioids: Taking MOGADON with opioid medicines can cause:

- **severe drowsiness**
- **decreased awareness**
- **breathing problems**
- **coma**
- **death**

Withdrawal:

- If you suddenly stop your treatment, lower your dose too fast, or switch to another medication, you can experience withdrawal symptoms that can range from mild symptoms to severe or life threatening. Some of your withdrawal symptoms can last for months after you stop MOGADON. For example, you may experience an increase in sleep difficulties (rebound insomnia) and/or increased daytime anxiety (rebound anxiety) for one or two days after discontinuing MOGADON.
- Your risk of going through withdrawal is higher if you are taking MOGADON for a long time or at high doses. However, symptoms can still occur if you are taking MOGADON as directed for a short period of time or slowly reducing the dose.
- The symptoms of withdrawal often resemble the condition that you are being treated for. After stopping your treatment, it may be hard to tell if you are experiencing withdrawal or a return of your condition (relapse).
- Tell your doctor **right away** if you experience any symptoms of withdrawal after changing or stopping your treatment.
  Severe symptoms of withdrawal include:
  - feeling like you cannot move or respond (catatonia)
  - severe confusion, shivering, irregular heartrate and excessive sweating (delirium tremens)
  - feeling depressed
  - feeling disconnected from reality (dissociation)
  - seeing or hearing things that are not there (hallucinations)
  - overactive behaviour and thoughts (mania)
  - believing in things that are not true (psychosis)
  - convulsions (seizures), including some that do not stop
  - thoughts or actions of suicide

  For other symptoms of withdrawal, see the **Serious side effects, how often they happen and what to do about them** table (below).
- To reduce your chances of going through withdrawal:
  - always contact your doctor before stopping or reducing your dose of MOGADON or changing medications
  - always follow your doctor's instructions on how to reduce your dose carefully and safely
  - tell your doctor **right away** if you experience any unusual symptoms after changing or stopping your treatment

MOGADON with Opioids: Taking MOGADON with opioid medicines can cause severe drowsiness and breathing problems.

- Tell your doctor if you:
  - are taking opioid medicines
  - are prescribed an opioid medicine after you start taking MOGADON
- Do NOT drive or operate heavy machinery or do tasks that require special attention until you know how taking an opioid medicine and MOGADON affects you.

Falls and Fractures: Benzodiazepines like MOGADON can cause you to feel sleepy, dizzy and affect your balance. This increases your risk of falling, which can cause fractures or other fall related-injuries, especially if you:

- take other sedatives
- consume alcohol
- are elderly or
- have a condition that causes weakness or frailty

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

leaving the house, making and eating food, talking on the phone, etc.

Important:
1. Do not take more MOGADON than prescribed.
2. Do not take MOGADON if you drink alcohol.
3. Talk to your doctor about all of your medicines, including over-the-counter medicines and herbal products. Your doctor will tell you if you can take MOGADON with your other medicines.
4. You and people close to you should watch for the type of unusual behaviour described above. If you find out that you have done *any* such activities for which you have no memory you should call your doctor immediately.

Mental Alertness:
MOGADON may affect your ability to be alert. DO NOT DRIVE A CAR or operate potentially dangerous machinery until you experience how this drug will affect you.

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 "traveler's amnesia". DO NOT TAKE MOGADON 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.

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, worsening insomnia and worsening depression, including suicidal thinking.

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

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.

Worsening of Side Effects:
DO NOT CONSUME ALCOHOL WHILE TAKING MOGADON. Some medicines may also worsen side effects that some patients experience with MOGADON (see "INTERACTIONS WITH THIS MEDICATION").

Effects on Pregnancy:
Certain benzodiazepine sleeping pills have been linked to birth defects when taken during pregnancy. In addition, benzodiazepine sleeping pills taken during the last weeks of pregnancy have been known to sedate the baby and may also cause withdrawal symptoms after birth. DO NOT TAKE MOGADON at any time during pregnancy.

BEFORE you use MOGADON talk to your doctor or pharmacist if:
- You have a lung disease or breathing problems.
- You have liver or kidney condition.
- You have a history of depression and/or suicide thoughts or attempts.
- You have had unexpected reactions to alcohol or sedative medications in the past, such as irritability, aggression, hallucinations, etc.
- You have ever had a problem with:
  - substance use, including prescribed or illegal drugs, or
  - alcohol

- You have ever had seizures or convulsions (violent uncontrollable shaking of the body with or without loss of consciousness)
- You are planning to become pregnant, you are pregnant, or you become pregnant while taking this medication.
- You are breastfeeding.
- You consume alcohol.
- You are taking other medicines, including drugs you can buy without a prescription.
- You have lactose intolerance.

INTERACTIONS WITH THIS MEDICATION

Serious Drug Interactions

Taking MOGADON and opioids may cause:
- **severe drowsiness**
- **trouble breathing**
- **coma**
- **death**

Nitrazepam may produce more pronounced side effects when co-administered with alcohol, other tranquilizers or sleeping pills, sedative antihistamines, narcotic analgesics (opioids) (see **Serious Warnings and Precautions** box), anticonvulsants, antipsychotics (neuroleptics), anesthetics, or antidepressant agents or psychotropic medications which themselves can make you sleepy.

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

Do not take MOGADON if you drink alcohol. DO NOT USE MOGADON along with other medications without first discussing this with your doctor.

PROPER USE OF THIS MEDICATION

Benzodiazepine sleeping pills are effective medications and are relatively free of serious problems when used for the short-term management of insomnia. 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.

Usual dose in Insomnia:
- MOGADON is a prescription medication intended to help you sleep. Follow your doctor's advice about how to take MOGADON, when to take it, and how long to take it.
- Your doctor will slowly decrease your dose and will tell you when to stop taking the medicine. Always follow your doctor's instructions on how to lower your dose carefully and safely to avoid experiencing withdrawal symptoms.

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.

DO NOT TAKE MOGADON if it is not prescribed for you.

DO NOT TAKE MOGADON for more than 7 to 10 days without first consulting your doctor. If you still have problems sleeping after you finish your tablets, contact your doctor again.

The lowest effective dose should be used.
DO NOT INCREASE THE PRESCRIBED DOSE.

Do not take MOGADON if you drink alcohol.

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

Do not drive a car or operate potentially dangerous machinery until you experience how MOGADON will affect you the next day.

MOGADON is not for use for insomnia in children under 18 years of age.

Overdose:
The principal manifestations of overdosage 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.

Contact your doctor, regional Poison Control Centre or pharmacist immediately if you suspect you have taken an overdose or someone else accidentally takes your MOGADON. If you are unable to contact them, go to a hospital emergency department for medical help, even though you may not feel sick. Show your doctor your bottle of tablets.

Missed Dose:
If you forget to take MOGADON Tablets, do not take a double dose to make up for the forgotten individual dose. Take the next dose at the usual time.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Common Side Effects:
Benzodiazepine sleeping pills may cause drowsiness, dizziness, light-headedness, 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.

DO NOT drink alcohol while using MOGADON. DO NOT USE MOGADON 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 dose possible that will still help you sleep at night. Benzodiazepines which are eliminated rapidly tend to cause less drowsiness the next day, but may cause withdrawal problems the day after use.

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

Rare cases of severe allergic reactions have been reported. Symptoms may include swelling of the tongue or throat, trouble breathing, and nausea and vomiting. Get emergency medical help if you get these symptoms after taking MOGADON.

Withdrawal-related side effects: See "WARNINGS AND PRECAUTIONS, Tolerance/Withdrawal Symptoms".

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

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
Rare	Unexpected reactions such as agitation, hyperactivity, excitement, hallucination, worsened insomnia, increased muscle spasticity, aggressiveness, irritability, rages, psychoses and violent behaviour		✓	
	Severe allergic reactions (swelling of the tongue or throat, trouble breathing, nausea and vomiting)			✓
	Depressed mood; thoughts of death or suicide		✓	
Very rare	Somnambulism (sleepwalking) – getting out of bed while not fully awake and do activities you do not remember the day after		✓	
Unknown	**Overdose:** extreme sleepiness, confusion, slurred speech, slow reflexes, slow shallow breathing, coma, loss of balance and coordination, uncontrolled rolling of the eyes, and low blood pressure.			✓
	Respiratory Depression: slow, shallow or weak breathing.			✓
	Withdrawal: Severe symptoms include: Catatonia: feeling like you cannot move or respond **Delirium Tremens:** severe confusion, shivering, irregular		✓	

	heartrate and excessive sweating **Feeling depressed** **Dissociation:** feeling disconnected from reality **Hallucinations:** seeing or hearing things that are not there **Mania:** overactive behaviour and thoughts **Psychosis:** believing in things that are not true **Convulsions:** (seizures – including some that do not stop): loss of consciousness with uncontrollable shaking **Thoughts or actions of suicide** **Other symptoms include:** Stomach cramps; trouble remembering or concentrating; diarrhea; feeling uneasy or restless; severe anxiety or panic-attacks; headache; sensitivity to light, noise or physical contact; shaking; vomiting; trouble sleeping; feeling irritable; muscle pain or stiffness; a burning or prickling feeling in the hands, arms,			
	legs or feet; sweating.			

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

HOW TO STORE IT

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

Keep out of reach of children.

Reporting Side Effects

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

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

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

MORE INFORMATION

If you want more information about MOGADON:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp). Find the Consumer Information on the manufacturer's website (https://www.aapharma.ca/en/products) or by calling 1-877-998-9097.

This leaflet was prepared by AA Pharma Inc.

Last revised: August 12, 2021