AUSTRALIAN PRODUCT INFORMATION – MOGADON (NITRAZEPAM) TABLETS

1 NAME OF THE MEDICINE

Nitrazepam

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Nitrazepam 5 mg tablets

Mogadon tablets contain lactose. For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Cylindrical, biplanar, white tablet. Imprint - upper face: "ICN" and two arcs, lower face: single break bar.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Insomnia, organic and inorganic in origin.

4.2 DOSE AND METHOD OF ADMINISTRATION

Adults: 1 to 2 tablets (5 to 10 mg) before retiring. This average dosage may be increased if necessary, up to 20 mg for in-patients.

Elderly patients: ½ to 1 tablet.

Children: Not recommended.

4.3 CONTRAINDICATIONS

- Patients with known hypersensitivity to benzodiazepines.
- Patients with chronic obstructive airway disease with incipient respiratory failure.
- Patients with severe hepatic insufficiency.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hypotension

Although hypotension has occurred only rarely, Mogadon should be administered with caution to patients in whom a drop in blood pressure might lead to cardiac or cerebral complications. This is particularly important in elderly patients (see Section 4.4 Use in the elderly).

Amnesia

Transient amnesia or memory impairment has been reported in association with the use of benzodiazepines.

Myasthenia gravis

Mogadon could increase the muscle weakness in myasthenia gravis and should be used with caution in this condition.

Acute narrow angle glaucoma

Caution should be used in the treatment of patients with acute narrow-angle glaucoma (because of atropine-like side effects).

Blood dycrasias

In rare instances some patients taking benzodiazepines have developed blood dyscrasias. As with other benzodiazepines periodic blood counts are recommended.

Depression, psychosis and schizophrenia

Mogadon is not recommended as primary therapy in patients with depression and/or psychosis. In such conditions psychiatric assessment and supervision are necessary if benzodiazepines are indicated. Benzodiazepines may increase depression in some patients and may contribute to deterioration in severely disturbed schizophrenics with confusion and withdrawal. Suicidal tendencies may be present or uncovered and protective measures may be required.

Paradoxical reactions

Paradoxical reactions such as restlessness, agitation, irritability aggressiveness, delusion, nightmares, psychoses, inappropriate behaviour and other adverse behavioural effects, acute rage, stimulation or excitement may occur. Should such reactions occur, Mogadon should be discontinued.

Impaired respiratory function

Caution in the use of Mogadon is recommended in patients with respiratory depression. In patients with chronic obstructive pulmonary disease, benzodiazepines can cause increased arterial carbon dioxide tension and decreased oxygen tension.

Epilepsy

Abrupt withdrawal of benzodiazepines in persons with convulsive disorders may be associated with a temporary increase in the frequency and/or severity of seizures.

Abuse

Caution must be exercised in administering Mogadon to individuals known to be addiction prone or those whose history suggests they may increase the dosage on their own initiative. It is desirable to limit repeat prescription without adequate medical supervision.

Dependence and tolerance

The use of benzodiazepines may lead to dependence, as defined by the presence of a withdrawal syndrome on discontinuation of the drug. Tolerance, as defined by a need to increase the dose in order to achieve the same therapeutic effect, seldom occurs in patients receiving recommended doses under medical supervision. Tolerance to sedation may occur with benzodiazepines, especially in those with drug seeking behaviour.

Duration of treatment

In general, benzodiazepines should be prescribed for short periods only (e.g. 2-4 weeks) see Section 4.2 Dosage and Administration. Continuous long-term use of Mogadon is not recommended. There is

evidence that tolerance develops to the sedative effects of benzodiazepines. After as little as one week of therapy, withdrawal symptoms can appear following the cessation of recommended doses (e.g. rebound insomnia following cessation of a hypnotic benzodiazepine).

Withdrawal

Withdrawal symptoms similar in character to those noted with barbiturates and alcohol have occurred following abrupt discontinuation of benzodiazepines. These symptoms range from insomnia, anxiety, dysphoria, palpitations, panic attacks, vertigo, myoclonus, akinesia, hypersensitivity to light, sound and touch, abnormal body sensations (e.g. feeling of motion, metallic taste), depersonalisation, derealisation, delusional beliefs, hyperreflexia and loss of short term memory, to a major syndrome which may include convulsions, tremor, abdominal and muscle cramps, confusional state, delirium, hallucinations, hyperthermia, psychosis, vomiting and sweating. Such manifestations of withdrawal, especially the more serious ones, are more common in patients who have received excessive doses over a prolonged period. However, withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines taken continuously at therapeutic levels. Accordingly, Mogadon should be terminated by tapering the dose to minimise occurrence of withdrawal symptoms. Patients should be advised to consult with their physician before either increasing the dose or abruptly discontinuing the medication.

Rebound phenomena have been described in the context of benzodiazepine use. Rebound insomnia and anxiety mean an increase in the severity of these symptoms beyond pre-treatment levels following cessation of benzodiazepines. Rebound phenomena in general possibly reflect re-emergence of pre-existing symptoms combined with withdrawal symptoms described earlier. Some patients prescribed benzodiazepines with very short half-lives (in the order of 2 to 4 hours) may experience relatively mild rebound symptoms in between their regular doses. Withdrawal/rebound symptoms may follow high doses for relatively short periods.

Dose tapering

Following the prolonged use of Mogadon at therapeutic doses, withdrawal from the medication should be gradual. An individualised timetable should be planned for each patient in whom dependence is known or suspected. Periods from four weeks to four months have been suggested. As with other benzodiazepines when treatment is suddenly withdrawn, a temporary increase in sleep disturbance can occur after use of Mogadon (see Section 4.4 Special Warnings and Precautions for Use - Dependence and tolerance).

Somnambulism and associated behaviours

Complex behaviours have been reported with sedative hypnotics. These events can occur in sedative-hypnotic naïve as well as in sedative-hypnotic experienced persons. These events can occur at normal therapeutic doses, and the risk appears to be increased when sedative-hypnotics are combined with alcohol or other CNS depressants or used at doses exceeding the maximum recommended dose. Discontinuation of sedative-hypnotics should be strongly considered for patients who have reported complex behaviours whilst not fully awake after taking a sedative-hypnotic.

Angioedema

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. Some patients have had additional symptoms such as dyspnoea, throat closing, or nausea and vomiting that suggest anaphylaxis. If

angioedema involves the tongue, glottis or larynx, airway obstruction may occur and be fatal and patients should be advised to contact the emergency department of their nearest hospital as soon as possible.

Use in hepatic impairment

Patients with impaired hepatic function should use benzodiazepine medication with caution and dosage reduction may be advisable. In rare instances some patients have had elevation of liver enzymes. As with other benzodiazepines periodic liver function tests are recommended.

Use in renal impairment

Patients with impaired renal function should use benzodiazepine medication with caution and dosage reduction may be advisable.

Use in the elderly

Geriatric or debilitated patients may be particularly susceptible to the sedative effects of benzodiazepines and associated giddiness, ataxia and confusion, which may increase the possibility of a fall.

In elderly, bed-ridden patients, bronchial hypersecretion and excessive salivation leading to aspiration/pneumonia may occur (see Section 8 Adverse Effects).

Paediatric use

Not approved for use as a hypnotic in children. (See also Section 4.8 Adverse Effects).

Effects on laboratory tests

Minor EEG changes, usually low voltage fast activity, of no known clinical significance has been reported with benzodiazepine administration.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

The benzodiazepines, including Mogadon, produce additive CNS depressant effects when co-administered with other medications which themselves produce CNS depression, e.g. barbiturates, alcohol, sedatives, tricyclic antidepressants, non-selective MAO inhibitors, phenothiazines and other antipsychotics, skeletal muscle relaxants, antihistamines, narcotic analgesics and anaesthetics (see Section 4.4. Special Warnings and Precautions for Use).

Mogadon undergoes oxidative metabolism, and consequently may interact with disulfiram or cimetidine resulting in increased plasma levels of Mogadon. Patients should be observed closely for evidence of enhanced benzodiazepine response during concomitant treatment with either disulfiram or cimetidine; some patients may require a reduction in benzodiazepine dosage.

The anticholinergic effects of other drugs including atropine and similar drugs, antihistamines and antidepressants may be potentiated.

Interactions have been reported between some benzodiazepines and anticonvulsants, with changes in the serum concentration of the benzodiazepine or anticonvulsant. It is recommended that patients be observed for altered responses when benzodiazepines and anticonvulsants are prescribed together, and that serum level monitoring of the anticonvulsant be performed more frequently.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available.

Use in pregnancy – Pregnancy Category C

Benzodiazepines cross the placenta and may cause hypotonia, reduced respiratory function and hypothermia in the newborn infant. Continuous treatment during pregnancy and administration of high doses in connection with delivery should be avoided. Withdrawal symptoms in newborn infants have been reported with this class of drugs.

Use in lactation

Caution should be exercised when Mogadon is given to nursing women. Mogadon is excreted in human breast milk and may cause drowsiness and feeding difficulties in the infant.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

As with all patients taking CNS-depressant medications, patients receiving Mogadon should be warned not to operate dangerous machinery or motor vehicles until it is known that they do not become drowsy or dizzy from Mogadon therapy. Abilities may be impaired on the day following use. Patients should be advised that their tolerance for alcohol and other CNS depressants will be diminished and that these drugs should either be eliminated or given in reduced dosage in the presence of Mogadon (see Section 4.5 Interactions with Other Medicines and Other Forms of Interactions).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Mogadon is usually well tolerated.

More common reactions: CNS depression including drowsiness, dizziness, fatigue, confusion, ataxia, impairment of memory, headache, hangover feeling in the morning, vertigo, slurred speech, decreased physical performance, numbed emotions, reduced alertness, muscle weakness, double vision and inattention have been reported. Unpleasant dreams and rebound insomnia have also been reported.

Less common reactions: Rarely hypotension, faintness, palpitation, rash or pruritus, gastrointestinal disturbances, changes in libido.

Very infrequently, paradoxical reactions may occur, e.g. excitement, stimulation, hallucinations, hyperactivity, and insomnia. Depressed or increased dreaming, disorientation, severe sedation, retrograde amnesia, headache, hypothermia, delirium tremens have also been reported.

Hypersecretion of saliva and bronchial mucus has occurred with doses of 0.7 mg/kg/day. In infants and young children, as well as in elderly, bed-ridden patients, bronchial hypersecretion and excessive salivation leading to aspiration/pneumonia may occur.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Symptoms

Overdosage of benzodiazepines is usually manifested by degrees of central nervous system depression ranging from drowsiness to coma. In mild cases, symptoms include drowsiness, mental confusion and lethargy. In more serious cases, symptoms may include ataxia, hypotonia, hypotension, respiratory depression, coma, and very rarely, death.

Treatment

In the management of overdosage with any medication, it should be borne in mind that multiple agents may have been taken.

Activated charcoal may reduce absorption of the drug if given within one to two hours of ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected. Cardiac and vital signs monitoring is recommended, along with general symptomatic and supportive measures. Hypotension and respiratory depression should be managed according to general principles.

Haemoperfusion and haemodialysis are not useful in benzodiazepine intoxication. The benzodiazepine antagonist flumazenil may be useful in hospitalised patients for the reversal of acute benzodiazepine effects. Please consult the flumazenil product information prior to usage.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Nitrazepam is a member of the group of benzodiazepine agonists and exhibits sedative, anxiolytic, anticonvulsant and muscle relaxant effects. This is presumed to be the result of facilitating the action in the brain of gamma aminobutyric acid, an endogenous inhibitor neurotransmitter.

Taken in the evening in recommended doses Mogadon induces sleep lasting 6-8 hours.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Nitrazepam is well and fairly rapidly absorbed from the GI tract. There is considerable interindividual variation in the rate of absorption with time to reach peak plasma concentrations following oral administration about 2 hours with a range of 0.5 - 5 hours. The drug crosses the CSF, the placenta and is excreted in milk.

Peak plasma levels following a 10 mg single oral dose are about 68 - 108 nanogram/mL and following a 5 mg single oral dose about 25 - 50 nanogram/mL. Twelve hours after oral administration of 5 mg nitrazepam, blood levels are about 12 - 38 nanogram/mL.

Bioavailability: In one study comparing oral with IV administration, bioavailability varied from 53% - 94% (average 78%).

Distribution

Nitrazepam is lipophilic and readily crosses body membranes.

CSF concentration of nitrazepam is about 10% total plasma level and similar to the protein free fraction in plasma. One study observed accumulation of nitrazepam in the CSF.

Nitrazepam is found in saliva at lower concentrations than protein free levels in serum.

Nitrazepam has been shown to cross the placenta and reach concentrations between 50 and 90% of the concentration in maternal plasma. It is excreted in breast milk.

The volume of distribution has been found to be significantly higher in elderly immobilised patients than in young controls, whereas the volume of distribution in healthy elderly subjects was found to be similar to young healthy subjects.

Protein Binding: Nitrazepam is approximately 87% bound to plasma protein.

Metabolism

Nitrazepam is metabolised to a significant extent by the liver and the primary route of elimination is urinary excretion of these metabolites. Thus, hepatic or renal disease may require alteration of nitrazepam dosage.

The major pathway is conversion to 7-aminonitrazepam and then to 7-acetamido-nitrazepam with subsequent hydroxylation. Opening of the diazepine ring to form 2-amino-5-nitrobenzophenone has also been reported. These metabolites have very weak pharmacological activity.

There is no evidence of nitrazepam dependent enzyme induction or inhibition during long term treatment.

Total plasma clearance has been estimated as 4.1 ± 2.0 litre/hour in young and 4.7 ± 1.5 litre/hour in elderly patients.

Excretion

Nitrazepam is mainly excreted as urinary metabolites. During the first 120 hours after a single radio-labelled 10 mg oral dose, the total renal elimination was 70%. Only 1% or less of the administered dose is excreted as unchanged nitrazepam.

The main urinary excretion products are free or conjugated 7-amino nitrazepam and 7-acetamido nitrazepam. Individual variation of the total excreted metabolites is high, ranging between 17 and 99% of the administered dose. Of this, the conjugated metabolites made up an average of 57%.

One faecal excretion study indicates the possibility of limited biliary excretion of the metabolites.

Half Life: Nitrazepam is eliminated relatively slowly from the body. Following oral administration, half-life has been estimated to be from 16 to 48 hours, average 27 hours. The half-life in CSF appears to be about twice as long as that in plasma.

Elimination half-life has been estimated to be significantly higher in elderly debilitated patients as opposed to healthy elderly subjects and young subjects.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

- lactose
- magnesium stearate
- starch – maize.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

PVC/PVDC/Aluminium Blister pack: 4's[#], 25's, 30's[#], 100's[#].

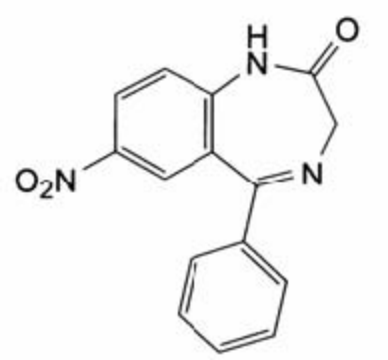
[#] not currently distributed in Australia

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



Chemically nitrazepam is 1,3-dihydro-7-nitro-5-phenyl-2H-1-benzodiazepine-2 one. It is a pale yellow, crystalline substance, insoluble in water. It has a molecular weight of 281.27.

CAS number

146-22-5

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 - Prescription Only Medicine

8 SPONSOR

iNova Pharmaceuticals (Australia) Pty Limited
Level 10, 12 Help Street
Chatswood NSW 2067

Telephone: 1800 630 056

9 DATE OF FIRST APPROVAL

30 June 1993

10 DATE OF REVISION

8 April 2019

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	Revised to the new Australian form for providing product information format and minor editorial changes.