New Zealand Data Sheet

1. PRODUCT NAME

Nitrados 5mg Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains nitrazepam 5mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Nitrados 5mg Tablet: circular, white, biconvex tablets with a diameter of 8.00mm, scored on one side and company DP logo on the other.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Nitrazepam is indicated in adults for:

- Short term treatment of insomnia when it is severe, disabling or subjecting the individual to unacceptable distress, where daytime sedation is acceptable.

4.2. Dose and method of administration

The underlying cause for insomnia should be sought before deciding the use of benzodiazepines for symptomatic relief.

The lowest effective dose should be used, and treatment should be intermittent if possible. Treatment duration should not extend beyond 4 weeks to prevent dependency, and treatment should be gradually withdrawn.

Long-term chronic use is not recommended. Patients who have received benzodiazepines for a long time may require an extended withdrawal period.

Dose

Adult:

5 to 10 mg before retiring.

Elderly:

2.5 mg – 5 mg before retiring, dose should not exceed half of the normal recommended dose for adults.

Children:

The use in children is not recommended.

Special populations:
In patients with chronic pulmonary insufficiency, and in patients with chronic renal or hepatic disease, dosage may need to be reduced.

Treatment duration

- For patients with insomnia the duration of treatment should not exceed 4 weeks (including the tapering off process).
- Continuous long term use is not recommended, but intermittent use may be appropriate.
- Where long-term therapy is considered essential, the patient should be regularly reviewed *(see section 4.4)*

Method of Administration
For oral administration

4.3. Contraindications

- Patients with known hypersensitivity to benzodiazepines or to any of the excipients listed in *section 6.1.*
- Use at high altitude where benzodiazepines may retard the hypoxic ventilatory response and exacerbate sleep hypoxaemia.
- Patients with head injuries, other acute neurological damage, existing CNS depression or coma.
- Myasthenia gravis, in which the additional muscle-relaxing effects of nitrazepam could have deleterious consequences.
- Acute pulmonary insufficiency, sleep apnoea and severe chronic obstructive airway disease with hypercapnia and incipient respiratory failure.
- Monotherapy to treat insomnia associated with depression, due to a risk of suicide *(see section 4.4).*
- Patients with chronic psychotic, phobic or obsessive behaviour.
- Patients with severe hepatic insufficiency.

4.4. Special warnings and precautions for use

Risks from concomitant use with opioids
Concomitant use of benzodiazepines, including nitrazepam, and opioids may result in profound sedation, respiratory depression, coma, and death. Because of these risks, reserve concomitant prescribing of benzodiazepines and opioids for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of

opioids alone. If a decision is made to prescribe nitrazepam concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use, and follow patients closely for signs and symptoms of respiratory depression and sedation. Advise both patients and caregivers about the risks of respiratory depression and sedation nitrazepam is used with opioids *(see section 4.5 Interactions with other medicines and other forms of interaction)*.

Tolerance
There is evidence that tolerance develops to the sedative effects of benzodiazepines.

Dependence and Withdrawal
Development of dependence is common after regular use of nitrazepam, particularly in patients with a history of drug or alcohol abuse or marked personality disorders. Dependence can occur even with therapeutic doses administered for short periods of time.

Discontinuation of nitrazepam therapy may result in withdrawal or rebound phenomena (*see section 4.8 for symptoms of benzodiazepine withdrawal*). Nitrazepam dose should be tapered off gradually to minimise the occurrence of the withdrawal symptoms. Regular monitoring of physical and psychological states in such patients is essential. Treatment should be given at the lowest therapeutic dose possible. Avoid routine repeat prescriptions, course of treatment should not exceed four weeks and it should be supplied intermittently.

Idiosyncratic reactions or psychiatric and/or paradoxical reactions
As with other benzodiazepines and CNS active drugs, three idiosyncratic symptom clusters, which may overlap, have been described.

- Amnestic symptoms, transient amnesia, anterograde amnesia with appropriate or inappropriate behaviour.
- Confusional states: disorientation, derealisation, depersonalization and/or clouding of consciousness.
- Agitational states: sleep disturbances, restlessness, irritability, aggression and excitation.

Nitrazepam should be discontinued if confusion or agitation occurs

Depression
Depression has been reported with therapeutic use and withdrawal of benzodiazepine therapy. The disinhibiting effects of benzodiazepines may also play a role in the precipitation of suicide attempts or completed suicides. Therefore,

benzodiazepines should not be used alone in treating depression with or without anxiety since it may induce suicide or aggressive behaviour.

Abuse
Nitrazepam should be used with caution in patients known to be prone to addiction. Because of a risk of abuse, repeat prescriptions should not be given without medical review.

Concomitant use with alcohol/CNS depressants
The concomitant use of nitrazepam with alcohol or/and CNS depressants should be avoided. Such concomitant use has the potential to increase the clinical effects of nitrazepam which may include severe sedation, clinically relevant respiratory and/or cardiovascular depression. It may also intensify any impairment in performing skilled tasks, and the individual response cannot be foreseen *(see section 4.5).*

Porphyria
Nitrazepam is porphyrinogenic in animal and in vitro studies.

Glaucoma
Use of benzodiazepines in acute closed-angle glaucoma is not advisable although the reasons for this are not clear.

Specific patient groups
- In patients with chronic pulmonary insufficiency, and in patients with chronic renal or hepatic disease, regular monitoring and dose reduction may be necessary, particularly in elderly patients with these conditions.
- Caution is indicated when cerebral arteriosclerosis or cardiorespiratory insufficiency is present.
- It may precipitate acute attacks in gout patients.
- Elderly patients are often particularly sensitive to centrally-acting drugs such as neuroleptics, tranquilizers, antidepressants, hypnotics, alcohol, antihistamines, opioid analgesics and general anaesthetics. If nitrazepam is combined with any of these drugs, their sedative effect may be intensified.

4.5. Interaction with other medicines and other forms of interaction

Opioids
The concomitant use of benzodiazepines and opioids increases the risk of respiratory depression because of actions at different receptor sites in the CNS that control respiration. Benzodiazepines interact at $GABA_A$ sites, and opioids interact primarily at mu receptors. When benzodiazepines and opioids are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory

depression exists. Limit dosage and duration of concomitant use of benzodiazepines and opioids, and follow patients closely for respiratory depression and sedation *(see section 4.4).*

Centrally-acting drugs
Nitrazepam potentiates the action of centrally active drugs eg, alcohol, neuroleptics, antidepressants, tranquillizers, sedatives, hypnotics, opioid analgesics, antihistamines and general anaesthetics, hence doses of any such combination should be reduced especially in elderly patients.

Anti-epileptics
Concomitant use with antiepileptics such as hydantoin or barbiturates or a combination containing these may increase side effects and toxicity. Careful dose adjustment in the initial treatment is required.

Cimetidine
Cimetidine is reported to inhibit metabolism of nitrazepam hence enhancing the effects of the latter.

4.6. Fertility, pregnancy and lactation

Pregnancy
First trimester: benzodiazepines in general are associated with unspecified embryopathy, foetopathy, unspecified congenital CNS and genitourinary malformations, cleft palate and cleft lip. The association cannot be confirmed by various studies.

Third trimester: high doses or prolonged low doses of benzodiazepines in the third trimester of pregnancy may cause foetal heart irregularities, neonatal drowsiness, respiratory depression and floppy infant syndrome characterised by hypotonia, hypothermia and poor sucking.

Infantile withdrawal symptoms and hyperbilirubinaemia have also been observed. In view of the above possible dangers, nitrazepam should only be given to women who are or may become pregnant when the potential benefit outweighs the potential risk.

Breast-feeding
Nitrazepam has been found in breast milk. Breast feeding mothers should avoid taking nitrazepam or alternative method of infant feeding should be used.

Fertility
No information is held on the effects of nitrazepam on fertility.

4.7. Effects on ability to drive and use machines

Dose-related drowsiness, amnesia, unsteadiness and impaired muscle function may adversely affect the ability to drive or to use machines. Patients should be advised that, like all medicines of this type, Nitrados may modify their performance at skilled tasks to a varying degree depending on dosage, administration and individual susceptibility. Patients should be further advised that alcohol may intensify any impairment and should be avoided during treatment.

4.8. Undesirable effects

Blood and lymphatic system disorders

Blood dyscrasia

Immune system disorders

Hypersensitivity reactions (anaphylaxis and angioedema)

Psychiatric disorders

Confusion, paradoxical aggression, excitement, libido fluctuations, restlessness, amnesic symptoms, agitation, unmasking of depression with suicidal tendencies *(see section 4.4)*

Nervous system disorders

Drowsiness, reduced alertness, unsteadiness, ataxia, dizziness, fatigue, headache (These symptoms are dose related and occur predominantly at the start of the therapy, they usually disappear with repeated administration). Increased dreaming has been reported early in treatment.

Eye disorders

Visual disturbances, double vision

Ear and labyrinth disorders

Vertigo

Vascular disorders

Hypotension

Respiratory, thoracic and mediastinal disorders

Respiratory depression

Fatal aspiration pneumonia in epileptic children has been reported

Hypersecretion of saliva and bronchial mucus

Gastrointestinal disorders
Gastrointestinal upset, swallowing difficulty

Hepatobiliary disorders
Jaundice

Skin and subcutaneous tissue disorders
Skin rashes

Renal and urinary disorders
Urinary incontinence or retention

Musculoskeletal and connective tissue disorders
Muscular weakness

Withdrawal: Symptoms of benzodiazepine withdrawal include anxiety, depression, impaired concentration, insomnia, headache, dizziness, tinnitus, loss of appetite, tremor, perspiration, irritability, perceptual disturbances such as hypersensitivity to physical, visual, and auditory stimuli and abnormal taste, nausea, vomiting, abdominal cramps, palpitations, mild systolic hypertension, tachycardia, and orthostatic hypotension (*see section 4.4*).

Rare and more serious symptoms include muscle twitching, confusional or paranoid psychosis, convulsions, hallucinations, and a state resembling delirium tremens. Broken sleep with vivid dreams and increased REM sleep may persist for some weeks after withdrawal of benzodiazepines.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected reactions https://nzphvc.otago.ac.nz/reporting/

4.9. Overdose

Symptoms
As with other benzodiazepines, overdose should not present a threat to life unless combined with other CNS depressants (including alcohol). Combination with other central-acting drugs and alcohol intensifies the overdose effect, which may be fatal if not treated.

Common features in nitrazepam overdose include drowsiness, confusion, ataxia, dysarthria and reduced reflexes. Deep coma or cardiorespiratory depression is rare unless in very severe cases, with anoxia and severe hypotension. Patients recovering from acute overdose may have insomnia and anxiety, with full-blown withdrawal syndrome, in particular convulsions, for those undergoing chronic benzodiazepine therapy.

Treatment

Treatment of overdose involves gastric lavage, symptomatic and general supportive measures. Dialysis is of little or no value. Flumazenil may be used as antidote, yet its role in reversing sedative effects of benzodiazepines is not clear.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic Group: hypnotics and sedatives, benzodiazepine derivatives
ATC code: N05CD

Mechanism of action

Nitrazepam, a 7-nitrobenzodiazepine, is an intermediate-acting benzodiazepine hypnotic with general anxiolytic, muscle relaxant, anticonvulsant and amnesic properties. Neuropharmacologic investigations on rats and rabbits show that nitrazepam induces sleep in a different way to barbiturates. The latter impose sleep by general inhibition of the activating system. Nitrazepam, in contrast, induces sleep by screening this system from external stimuli.

Nitrazepam binds to the benzodiazepine binding site on the γ-aminobutyric acid (GABA) receptor protein complex. By allosteric interactions, this enhances binding of GABA to its own binding site, which activates direct opening of the chloride ion channel. As a result, this causes selective inhibition of overactive nerves coming in to the activating system, which, in turn, is responsible for the sleep disturbance. These overactive nerves come in particular from the substrate of emotional behaviour in the limbic system, thalamus and hypothalamus. Selective inhibition of emotional stimuli prevents disturbance of sleep-waking regulation, which should thus proceed normally. As a result, total sleeping time increases. Deep sleep and REM sleep are suppressed and replaced by relatively light sleep.

5.2. Pharmacokinetic properties

Absorption:

Nitrazepam is rapidly absorbed from the GI tract at a proportion of about 80% achieving initial peak plasma concentrations of between 28.2-45.0ng/ml after 30-240 minutes (mean about 80 minutes). It is also rapidly removed from the circulation into extra-cellular spaces. In normal subjects after taking an evening dose of 5-10mg, onset of sleep usually takes place within 30-60 minutes lasting for 6-8 hours.

Distribution:

Nitrazepam passes the blood brain barrier, placental barrier and traces are excreted into breast milk. The therapeutic serum level is about 40ng/ml and protein binding is about 85%.

Metabolism:

Metabolism of nitrazepam occurs in the liver involving nitroreduction and acetylation, the latter being subject to genetic polymorphism. The metabolites, which are inactive, are then excreted in the urine (free or conjugated) with little of the parent drug appearing unchanged (5%). About 20% of an oral dose is excreted in faeces.

Elimination:

The elimination half-life has been measured at between 18-36 hours, averaging about 24 hours, with steady state plasma levels of about 40-60ng/ml achieved within 4-5 days.

5.3. Preclinical safety data

No preclinical safety data is held for nitrazepam.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Each 5 mg tablet contains the following excipients:
Lactose monohydrate, maize starch and magnesium stearate.

6.2. Incompatibilities

None known.

6.3. Shelf life

36 months from date of manufacture.

6.4. Special precautions for storage

Store at or below 30°C.

Protect from light.

6.5. Nature and contents of container

Nitrazepam tablets are contained in a HDPE Plastic bottle.

Pack size of 100 tablets.

6.6. Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine

Class C5 Controlled Drug

8. SPONSOR

Douglas Pharmaceuticals Ltd

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New Zealand

Phone: (09) 835 0660

9. DATE OF FIRST APPROVAL

30 August 1979

10. DATE OF REVISION OF THE TEXT

23 May 2017

Summary table of changes

Sections changed	Summary of new information
	Update to the SmPC format
4.1	Removal of indication for epilepsy in children and adults Updated indication to insomnia from nervous sleep disturbance

4.2	Removal of dosage for children due to indication removal
4.3	Added ‘patients with chronic psychotic, phobic or obsessive behaviour’ and ‘patients with severe hepatic insufficiency’ as contraindications
4.4 & 4.5	Updated safety information on the risk from concomitant use with opioids
4.6	Added subsection on fertility
4.7	Updated safety information on the effects on ability to drive and use machines
4.8	Adverse effects are organised according to System Organ Class
6.6	Updated information on special precautions for disposal