

# DATA SHEET

## NITRADOS

Nitrazepam BP 5mg tablet

### Presentation

Circular, white, biconvex tablets with a diameter of 8.00mm, scored on one side and company logo on the other.

### Uses

#### *Actions*

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  $\gamma$ -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.

#### *Pharmacokinetics*

NITRADOS 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.

NITRADOS 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 of NITRADOS 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. 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.

## ***Indications***

Nervous sleep disturbances due to irritability, overwork, conflicts, travelling, anxiety, worry, tension and stress. Organic sleep disturbances in conjunction with specific therapy. Also used in epilepsy, notably for infantile spasms with hypsarrhythmia, infantile myoclonic seizures.

## **Dosage and Administration**

NITRADOS tablets are to be administered orally. It is recommended that treatment be short term to prevent dependency.

### ***Adult***

**For Hypnosis:** 5-10mg before retiring. This may be increased to 20mg for hospitalised patients.

**For Chronic Epilepsy:** Average dose 0.5mg/kg per day.

### ***Paediatric***

**Infantile spasms with hypsarrhythmia:** Maximum 3.0mg/kg body weight per day.

**For Chronic Epilepsy:** Average dose 1.0mg/kg per day.

### ***Geriatric***

2.5mg - 5mg before retiring

## **Contraindications**

Patients with known sensitivity to benzodiazepines.

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 NITRADOS could have deleterious consequences.

Also acute pulmonary insufficiency sleep apnoea and severe chronic obstructive airway disease with hypercapnia and incipient respiratory failure.

## **Warnings and Precautions**

### ***General***

Transient amnesia or impaired memory.

### ***Use in Pregnancy and Lactation***

**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, NITRADOS should only be given to women who are or may become pregnant when the potential benefit outweighs the potential risk.

**Nursing mothers** should avoid taking NITRADOS during lactation or use infant formula since NITRADOS has been found in breast milk.

### ***Use with Alcohol***

Patients should avoid taking alcohol while under the influence of treatment with NITRADOS since alcohol may intensify any impairment in performing skilled tasks and the individual response cannot be foreseen.

### ***Use when Operating Machinery***

Patients should avoid operating machinery of any sort or driving while taking NITRADOS as it may modify their reactions to a varying extent depending upon the dosage, administration and individual susceptibility.

### ***Use in Psychiatric Conditions***

As for diazepam, NITRADOS should not be used alone in treating depression with or without anxiety since it may induce suicide or aggressive behaviour. NITRADOS should not be used to treat chronic psychotic, phobic or obsessive behaviour.

### ***Use in Chronic Pulmonary Insufficiency, Renal or Hepatic Diseases***

Regular monitoring and dose reduction may be necessary particularly in elderly patients with these problems.

### ***Use in the Elderly***

Elderly patients are often particularly sensitive to central-acting drugs such as neuroleptics, tranquillizers, antidepressants, hypnotics, alcohol, antihistamines, opioid analgesics and general anaesthetics. If NITRADOS is combined with any of these drugs, their sedative effect may be intensified.

The dose of NITRADOS for elderly patients should be half of the normal adult dose at maximum. Caution is indicated when cerebral arteriosclerosis or cardiorespiratory insufficiency is present.

### ***Excessive, Prolonged Use***

This may result in psychological dependence with withdrawal symptoms such as depression, nervousness, rebound insomnia, irritability, perspiration and diarrhoea on abrupt discontinuation of NITRADOS.

This phenomenon is common in patients having marked personality disorders, alcoholism and drug abuse. Rarely confusion and convulsion may develop following withdrawal of excessive

dosages. Patients with a recent history of myocardial infarction may develop complete obstructive sleep apnoea on chronic use of benzodiazepines.

### **Management**

- Regular monitoring of physical and psychological states.
- Avoid routine repeat prescriptions, but give intermittently and not exceeding four weeks.
- Gradually withdraw treatment by tapering doses.
- Give the lowest therapeutic dose possible.

### **Use in Miscellaneous Cases**

Nitrazepam is porphyrinogenic in animal and *in vitro* studies. It may precipitate acute attack in gout patients. Use of benzodiazepines in acute closed-angle glaucoma is not advisable although the reasons for this are not clear.

### **Adverse Effects**

NITRADOS is usually well tolerated although the following side effects may occur: dose-related drowsiness, unsteadiness and ataxia. Less frequently headache, confusion, vertigo, dizziness, muscular weakness, changed libido, urinary incontinence or retention, skin rashes, visual and gastrointestinal upset and tiredness may be experienced. Blood dyscrasia, jaundice and hypersensitivity occur occasionally. In rare cases paradoxical aggression, excitement, restlessness, confusion and unmasking of depression with suicidal tendencies may occur. Swallowing difficulty and fatal aspiration pneumonia in epileptic children has been reported. Increased dreaming has been reported early in treatment.

Hypersecretion of saliva and bronchial mucus has occurred with doses over 0.7mg/kg per day.

### **Interactions**

NITRADOS potentiates the action of centrally active drugs eg. alcohol, neuroleptics, antidepressants, tranquilizers, sedatives, hypnotics, opioid analgesics, antihistamines and general anaesthetics, hence doses of any such combination should be reduced especially in elderly patients. 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 is reported to inhibit metabolism of nitrazepam hence enhancing the effects of the latter. Nitrazepam does not affect the elimination of warfarin or tricyclic antidepressants, nor does it promote excretion of 6 $\beta$ -hydroxycortisol.

### **Overdosage**

Common features in nitrazepam overdosage 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 overdosage may have insomnia and anxiety, with full-blown withdrawal syndrome, in particular convulsions, for those undergoing chronic benzodiazepine therapy.

Combination with other central-acting drugs and alcohol intensifies the overdose effect, which may be fatal if not treated.

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.

## Pharmaceutical Precautions

NITRADOS 5mg tablets can degrade to its quinoline derivative in the dry state and mainly to its benzophenone by hydrolysis in humid condition. It has a shelf-life of three years at room temperature.

Store at room temperature in well-closed containers. Protect from light and keep away from children's reach.

## Medicine Classification

Controlled Drug C5.

## Package Quantities

NITRADOS 5mg tablets: In packs of 100's in HDPE bottles.

## Further Information

Nitrazepam is a 7-nitrobenzodiazepine namely, 1,3-dihydro-7-nitro-5-phenyl-2H-1,4-benzodiazepin-2-one. Its molecular formula and weight are  $C_{15}H_{11}N_3O_3$  and 281.3 respectively.

LD<sub>50</sub> orally in rats is  $825 \pm 80\text{mg kg}^{-1}$ .

Other ingredients of the tablets are: Maize cornflour, Lactose and Magnesium stearate.

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