

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Nitrazepam 5 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg of Nitrazepam

Excipient with known effect: Each tablet contains 445 mg of Lactose.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablets.

Uncoated white flat bevel edged tablets with breakline on one face and stamped "SPN5" on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

Benzodiazepines are not recommended for the primary treatment of psychotic illness.

4.2 Posology and method of administration

Posology:

Adults: 5mg before retiring. This dose may, if necessary, be increased to 10mg.

Elderly: *Elderly or debilitated patients:* the elderly or patients with impaired renal and/or hepatic function will be particularly susceptible to the adverse

effects of Nitrazepam. Doses should not exceed half those normally recommended.

If organic brain changes are present, the dosage of Nitrazepam should not exceed 5mg in these patients.

Other Populations

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

Paediatric population

Nitrazepam tablets are contraindicated for use in children.

Dosage should be adjusted on an individual basis. Treatment should, if possible, be on an intermittent basis.

Treatment should be as short as possible and should be started with the lowest recommended dose. The maximum dose should not be exceeded. Generally the duration of treatment varies from a few days to two weeks with a maximum of four weeks; including the tapering off process. Patients who have taken Benzodiazepines for a prolonged time may require a longer period during which doses are reduced. Specialist help may be appropriate. Little is known regarding the efficacy or safety of benzodiazepines in long-term use.

In certain cases extension beyond the maximum treatment period may be necessary, if so, it should not take place without re-evaluation of the patient's status. Long-term chronic use is not recommended. 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 decreased. Moreover, it is important that the patient should be aware of the possibility of rebound phenomena (see *Undesirable Effects*) thereby minimising anxiety over such symptoms should they occur while the medicinal product is being discontinued. Nitrazepam therapy should not be stopped abruptly, but the dose tapered off.

The product should be taken just before going to bed.

In addition, for long acting benzodiazepines, it must be stated that the patient should be checked regularly at the start of treatment in order to decrease, if necessary, the dose or frequency of administration to prevent overdose due to accumulation.

Method of administration:

Tablets are for oral administration.

4.3 Contraindications

Hypersensitivity to the active substance, benzodiazepines, nitrazepam or to any of the excipients listed in section 6.1.

Hypersensitivity reactions with the benzodiazepines including rash, angioedema and hypertension have been reported on rare occasions in susceptible patients.

Use of this drug is also contraindicated in patients with severe respiratory insufficiency, short-term treatment of insomnia in children and juveniles, acute pulmonary insufficiency; respiratory depression; phobic or obsessional states; chronic psychosis; myasthenia gravis; sleep apnoea syndrome; severe hepatic insufficiency; use in children.

4.4 Special warnings and precautions for use

In patients with chronic pulmonary insufficiency, and in patients with chronic renal or hepatic disease, dosage may need to be reduced. Benzodiazepines are contraindicated in patients with severe hepatic insufficiency.

Nitrazepam should not be used alone to treat depression or anxiety associated with depression, since suicide may be precipitated in such patients.

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

Benzodiazepines should be used with extreme caution in patients with a history of alcohol or drug abuse. Benzodiazepines are not recommended for the primary treatment of phobic or obsessional states, chronic psychosis or psychotic illness.

Concomitant use of Nitrazepam and opioids may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing of sedative medicines such as benzodiazepines or related drugs such as Nitrazepam with opioids should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Nitrazepam concomitantly with opioids, the lowest effective dose should be used, and the duration of treatment should be as short as possible (see also general dose recommendation in section 4.2).

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers (where applicable) to be aware of these symptoms (see section 4.5).

If the patient is awoken during the period of maximum drug activity, recall may be impaired.

In cases of loss or bereavement, psychological adjustment may be inhibited by benzodiazepines.

Use of Benzodiazepines may lead to the development of physical and psychological dependence upon these products. The risk of dependence increases when high doses are used, especially when given over long periods. This is particularly so in patients with a history of alcoholism or drug abuse or in patients with marked personality disorders. Regular monitoring in such patients is essential; routine repeat prescriptions should be avoided and treatment should be withdrawn gradually. Symptoms such as depression, headaches, muscle weakness, nervousness, extreme anxiety, tension, restlessness, confusion, mood changes, rebound insomnia, irritability, sweating, and diarrhoea have been reported following abrupt cessation of treatment in patients receiving even normal therapeutic doses for short periods of time.

When benzodiazepines with a long duration of action are being used it is important to warn against changing to a benzodiazepine with a short duration of action, as withdrawal symptoms may develop.

In severe cases the following symptoms may occur: derealisation, depersonalisation, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact and hallucinations or epileptic seizures. In rare instances, withdrawal following excessive dosages may produce confusional states and psychotic manifestations and convulsions. Abuse of the benzodiazepines has been reported.

Tolerance: Some loss of efficacy to the hypnotic effects of short-acting benzodiazepines may develop after repeated use for a few weeks.

Rebound insomnia and anxiety:

A transient syndrome whereby the symptoms that led to treatment with a benzodiazepine recur in enhanced form, rebound insomnia may occur on withdrawal of hypnotic treatment. It may be accompanied by other reactions including mood changes, anxiety or restlessness. Since the risk of withdrawal phenomena and rebound phenomena is greater after abrupt discontinuation of treatment, it is recommended that the dosage be decreased gradually.

Abnormal psychological reactions to benzodiazepines have been reported. Rare behavioural effects include paradoxical aggressive outbursts, excitement, confusion, restlessness, agitation, irritability, delusion, rages, nightmares,

hallucinations, psychoses, inappropriate behaviour and the uncovering of depression with suicidal tendencies. Extreme caution should therefore be used in prescribing benzodiazepines to patients with personality disorders. If any of these reactions occur, use of the drug should be discontinued. These reactions may be quite severe and are more likely to occur in the elderly.

Benzodiazepines may induce anterograde amnesia. The condition usually occurs 1 to 2 hours after ingesting the product and may last up to several hours. Therefore, to reduce the risk, patients should ensure that they will be able to have an uninterrupted sleep of 7 to 8 hours.

Due to the myorelaxant effect there is a risk of falls and consequently of hip fractures particularly for elderly patients when they get up at night.

Concomitant use of 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 possibly including severe sedation, clinically relevant respiratory and/or cardiovascular depression (see section 4.5).

Special patient groups

An increase in intensity and incidence of CNS toxicity with age has been observed, especially at high doses. Therefore the dosage of Nitrazepam should not exceed 5 mg in elderly patients (see section 4.2). Due to the myorelaxant effect there is a risk of falls and consequently of hip fractures particularly for elderly patients when they get up at night.

In patients with chronic pulmonary insufficiency, and in patients with chronic renal or hepatic disease, dosage may need to be reduced. Benzodiazepines are contraindicated in patients with severe hepatic insufficiency.

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

In cases of loss or bereavement, psychological adjustment may be inhibited by benzodiazepines.

Pre-existing depression may emerge or worsen during use of benzodiazepines including nitrazepam. The use of benzodiazepines may unmask suicidal tendencies in depressed patients and should not be used without adequate antidepressant therapy.

Important information regarding the ingredients of this tablet

Lactose: Nitrazepam contains lactose. Patients with rare hereditary problems of galactose intolerance, the total lactase deficiency or glucose-galactase malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Enhancement of the central depressive effect may occur if benzodiazepines are combined with centrally-acting drugs such as neuroleptics, barbiturates, antipsychotics, tranquillisers, antidepressants, hypnotics, anxiolytics, analgesics and anaesthetics, anticonvulsants, anti-epileptics, sedative antihistamines, antihypertensives and beta-blockers. In the case of narcotic analgesics, enhancement of the euphoria may also occur, leading to an increase in psychological dependence. The elderly require special supervision.

The concomitant use of sedative medicines such as benzodiazepines or related drugs such as Nitrazepam with opioids increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dosage and duration of concomitant use should be limited (see section 4.4).

When Nitrazepam is used in conjunction with anti-epileptic drugs, side effects and toxicity may be more evident, particularly with hydantoins or barbiturates or combinations including them. This requires extra care in adjusting dosage in the initial stages of treatment.

Known inhibitors of hepatic enzymes, particularly cytochrome P450 have been shown to reduce the clearance of benzodiazepines e.g. cimetidine, someazole antifungal agents, omeprazole, anti-retroviral protease inhibitors, macrolide antibiotics, calcium channel blockers, selective serotonin reuptake inhibitors (SSRIs), and disulfiram and may potentiate their action and known inducers of hepatic enzymes, e.g. rifampicin or St. John's wort, may increase the clearance of benzodiazepines.

Concomitant intake with alcohol should be avoided. The sedative effect may be enhanced when the product is used in combination with alcohol. This adversely affects the ability to drive or use machines.

Concomitant administration of theophylline or aminophylline may reduce the sedative effects of benzodiazepines.

Concomitant intake of benzodiazepines with sodium oxybate may increase the effect of sodium oxybate.

Concomitant intake of valerian may increase or decrease the effect of nitrazepam.

4.6 Fertility, pregnancy and lactation

Pregnancy:

Nitrazepam crosses the placental barrier. The fetomaternal ratio of plasma concentration in early pregnancy is about 0.6 and in late pregnancy about 0.9. There are limited data of the use of nitrazepam in pregnant women. There have been isolated reports of very large doses of nitrazepam causing congenital abnormalities in humans.

Studies in animals have shown reproductive toxicity (see section 5.3)

High doses of nitrazepam during early pregnancy resulted in malformations in rats but not in mice.

Do not use during pregnancy, especially during the first and last trimesters, unless there are compelling reasons.

If the product is prescribed to a woman of childbearing potential, she should be warned to contact her physician regarding discontinuance of the product if she intends to become or suspects that she is pregnant.

Administration of benzodiazepines in the last trimester of pregnancy or during labour has been reported to produce irregularities in the foetal heart rate, and hypotonia, poor sucking, hypothermia and moderate respiratory depression in the neonate.

Infants born to mothers who took benzodiazepines chronically in the latter stages of pregnancy may have developed physical dependence and may be at some risk of developing withdrawal symptoms in the postnatal period.

Breast-feeding:

Since benzodiazepines are found in the breast milk, the use of Nitrazepam in mothers who are breast-feeding should be avoided.

Fertility:

Human data are not available. In investigations with mice and rats, Nitrazepam showed an impairment of spermatogenesis in male animals.

4.7 Effects on ability to drive and use machines

Patients should be advised that, like all medicaments of this type, nitrazepam may modify patients' performance at skilled tasks. Sedation, amnesia, impaired concentration and impaired muscle function may adversely affect the ability to drive or to use machinery. If insufficient sleep duration occurs, the likelihood of impaired alertness may be increased. Patients should further be advised that alcohol may intensify any impairment, and should therefore be avoided during treatment.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you
- It is an offence to drive while under the influence of this medicine
- However, you would not be committing an offence (called 'statutory defence') if:
 - The medicine has been prescribed to treat a medical or dental problem and
 - You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
 - It was not affecting your ability to drive safely

4.8 Undesirable effects

Within the system organ classes, adverse drug reactions are listed under heading of frequency (number of patients expected to experience the reaction, using the following convention:

Very common ($>1/10$) : common ($>1/100$ to $<1/10$); uncommon ($>1/1,000$ to $>1/100$); rare ($>1/10,000$ to $>1/1,000$); very rare ($<1/10,000$); not known (cannot be estimated from available data)

Blood and lymphatic system disorders:

Frequency not known: Blood disorder

Immune system disorders:

Frequency not known: Allergic skin reaction, anaphylactic reaction, angioedema

Psychiatric disorders:

Common: Numbed emotions, confusion state, depression (pre-existing depression may be unmasked).

Rare: Libido disorder

Frequency not know: Emotional disorder, delirium, insomnia, cognitive impairment, physical and psychological dependence (even at therapeutic doses), withdrawal syndrome accompanies by reactions including mood

changes, anxiety, and restlessness, drug abuse, agitation, aggression, delusion, anger, nightmare, hallucination, psychotic disorder.

Since the risk of withdrawal/rebound phenomena is greater after abrupt discontinuation of treatment, it is recommended that the dosage be decreased gradually.

Nervous system disorders:

Common: Drowsiness, reduced alertness, headache, dizziness

Rare: Vertigo, dysarthria

Frequently not known: Balance disorder, hypokinesia, tremor, anterograde amnesia, epilepsy.

The elderly are particularly sensitive to the effects of centrally-depressant drugs.

Eye disorders:

Common: Diplopia

Rare: Visual impairments

Vascular disorders:

Rare: Hypotension

Respiratory, thoracic and mediastinal disorders:

Frequency not known: Respiratory depression, increased bronchial secretion

Gastrointestinal disorders:

Rare: Abdominal discomfort, nausea

Hepatobiliary disorders:

Frequency not known: Jaundice

Skin and subcutaneous tissue disorders:

Rare: Skin rashes

Frequency not known: Urticaria, pruritus, dermatitis, erythema multiforme, Stevens-Johnson syndrome

Musculoskeletal and connective tissue disorders:

Common: Muscle weakness

Frequency not known: Muscle spasm

Due to the myorelaxant effect there is a risk of falls and consequently fractures in the elderly

Renal and urinary disorders:

Rare: Urinary retention

General disorders and administration site conditions:

Common: Fatigue, ataxia

Frequency not known: Irritability, rebound effect

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

When taken alone in overdose Nitrazepam presents few problems in management and should not present a threat to life unless combined with other CNS depressants (including alcohol).

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

Symptoms:

Overdose 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, dysarthria and lethargy, in more serious cases, symptoms may include ataxia, hypotonia, hypotension, respiratory depression, rarely coma and very rarely death.

Management:

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 oral benzodiazepines, 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, can be given within 1 hour of ingesting a significant quantity, provided the patient is awake and the airway is protected.

Special attention should be paid to respiratory and cardiovascular functions in intensive care. The value of dialysis has not been determined. Flumazenil is a specific IV antidote for use in emergency situations. Patients requiring such intervention should be monitored closely in hospital (see separate prescribing information).

The benzodiazepine antagonist flumazenil is not indicated in patients with epilepsy who have been treated with benzodiazepines. Antagonism of the benzodiazepine effect in such patients may trigger seizures.

If excitation occurs, barbiturates should not be used.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Hypnotics and Sedatives, Benzodiazepine derivatives,

ATC Code: N05CD02

Nitrazepam is a benzodiazepine compound with sedative properties. It acts in 30 to 60 minutes to produce sleep lasting 6 to 8 hours.

Nitrazepam binds to specific benzodiazepine receptors located on GABA-ergic neurons and potentiates the inhibitory actions of GABA-ergic neurons in the nervous system. After prolonged treatment, development of tolerance has been observed. Chronic benzodiazepine use leads to compensating changes in the central nervous system. GABAA receptors may become less responsive to the continuing acute effects of benzodiazepines, either as a result of adaptation in the GABAA receptor itself, intracellular mechanisms, or changes in the neurotransmitter systems. Probably multiple adaptive mechanisms simultaneously coexist.

An increase in intensity and incidence of CNS toxicity with age has been observed, especially at high doses. Therefore the dosage of Nitrazepam should not exceed 5 mg in elderly patients (see section 4.2). The increased CNS toxicity in elderly seems to be the result of the combination of pharmacokinetic and pharmacodynamic factors.

Under the treatment with Nitrazepam, especially with 10 mg, impairment of psychomotor and cognitive performance was observed in several investigations. Especially the driving ability is affected (see section 4.7)

Psychomotor impairment increased with duration of treatment. In elderly patients the effect is more pronounced.

5.2 Pharmacokinetic properties

Absorption:

Nitrazepam is well absorbed from the GI tract with peak blood levels being achieved within two hours of administration. Two hours after administration, the concentration of nitrazepam in the cerebrospinal fluid is about 8% and after 36 hours approximately 16% of the concentration in the plasma. The cerebrospinal fluid concentration thus corresponds to the non-protein-bound fraction of active ingredient in the plasma. Steady-state levels are achieved within 5 days. Bioavailability after oral intake is about 80% with remarkable intraindividual variation (53% to 97%). Results concerning influence of food on nitrazepam absorption are inconsistent. Food may cause a decrease and delay in absorption (up to 30%).

Distribution:

The protein binding of nitrazepam is about 85% to 88% in adults and children. In younger persons the volume of distribution is 2-2.5 L/kg, in elderly patients the volume of distribution is greater (4.8 L/kg).

The distribution half-life is about 15 minutes. Maximum serum concentrations of 35-40 ng/ml are achieved after oral intake of 5 mg Nitrazepam. The percentage ratio between the mean concentration in cerebrospinal fluid and in plasma increased from 8.0% at 2 hours to 15.6% at 36 hours. The cerebrospinal fluid concentration thus corresponds to the non-protein-bound fraction of active ingredient in the plasma. Nitrazepam crosses the placental barrier. The fetomaternal ratio of plasma concentration is about 0.6 in early pregnancy and about 0.9 in late pregnancy. Nitrazepam can be found in breast milk. The milk to plasma ratio is about 0.3. The pharmacokinetics of Nitrazepam can be described as two-compartment open model.

Biotransformation:

The main metabolic pathway consists of reduction and further acetylation of the 7-nitro group. The main metabolites are 7-aminonitrazepam and 7-acetamidonitrazepam which are both clinically inactive. In the metabolism of nitrazepam CYP3A4 and CYP2D6 are involved. Nitrazepam is neither an inducer nor an inhibitor of metabolic enzymes.

Elimination:

About 5% of the metabolites are excreted unchanged in the urine together with less than 10% each of the 7-amino- and 7-acetylamino- metabolites in the first 48 hours. In younger persons the volume of distribution is 2L/kg, in elderly

patients the volume of distribution is greater and the mean elimination half-life rises to 40 hours.

The half-life is on average 24 hours. In the cerebrospinal fluid the half-life is about 70 hours. Nitrazepam is mainly excreted as urinary metabolites, about 60% are conjugated. Steady-state levels are achieved within 5 days.

Pharmacokinetic/ Pharmacodynamic relationship:

No clear correlation has been demonstrated between the blood levels of nitrazepam and its clinical effects.

5.3 Preclinical safety data

Developmental toxicity:

Developmental toxicity studies in mouse, rat, rabbit and dog were performed. At the 100 mg/kg/day dose in the rat and rabbit, multiple skeletal defects (rat) and foetal resorptions (rat and rabbit) were produced. Nitrazepam appears to produce a doserelated teratogenic effect in the rat with a teratogenic threshold of around 30 mg/kg/day.

Nitrazepam was not teratogenic in mice. The lack of teratogenic effect observed in mice may be due to lower N-acetyltransferase and deacetylase activities in mice and subsequent lack of metabolism to the metabolite AANZ which may be involved in the teratogenic mechanism.

Reproductive toxicity:

Nitrazepam impaired spermatogenesis in male rats.

Carcinogenicity:

No carcinogenicity studies have been conducted with nitrazepam. However there was no indication of a carcinogenic effect in chronic toxicity studies in rats and dogs.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose
Starch
Talc
Stearic acid

6.2 Incompatibilities

None Known

6.3 Shelf life
5 Years

6.4 Special precautions for storage
Do not store above 25°C. Store in the original container.

6.5 Nature and contents of container
The product is available in packs of 50, 500, and 1000 tablets in Securitainers.

The container is made up of High Density Polypropylene body and Low Density Polyethylene cap.

6.6 Special precautions for disposal

No special requirements for disposal

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 17907/0355

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30/04/2024

