# Nitrazepam 5 mg Tablets

Summary of Product Characteristics Updated 12-Feb-2020 | Accord-UK Ltd

## 1. Name of the medicinal product

Nitrazepam 5mg tablets

## 2. Qualitative and quantitative composition

Each tablet contains 5mg of nitrazepam.

Excipients with known effect:

Each tablet contains 504.17mg lactose

For the full list of excipients, see section 6.1.

## 3. Pharmaceutical form

Tablet.

White, circular, flat bevelled-edge uncoated tablets impressed “C” and the identifying letters “NA” on either side of a central division line on one face.

## 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

**Adults**

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

**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:*

Nitrazepam tablets are for oral administration.

**4.3 Contraindications**

• Patients with hypersensitivity to 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:

- acute pulmonary insufficiency;

- respiratory depression;

- phobic or obsessional states;

- chronic psychosis;

- myasthenia gravis;

- sleep apnoea syndrome;

- severe hepatic insufficiency;

- use in children.

- acute porphyria

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

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

Tolerance to their effects develops within 3-14 days of continuous use and hence treatment regimes should be kept to a minimum and repeat prescriptions avoided. Limits of tolerance in patients with organic cerebral changes (particularly resulting from arteriosclerosis) or cardiorespiratory insufficiency may be very wide; care must be taken in adapting the dosage with such patients.

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.

Hypoalbuminaemia (may predispose patient to higher incidence of sedative side effects).

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose 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, tranquillisers, antidepressants, hypnotics, analgesics and anaesthetics, anti-epileptics, sedative antihistamines, lofexidine and nabilone. 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 cythochrome P450 have been shown to reduce the clearance of benzodiazepines and may potentiate their action and known inducers of hepatic enzymes, e.g. rifampicin, 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.

Enhances sedative effect with moxonidine.

Baclofen and tizanidine (enhanced sedative effect).

**4.6 Fertility, pregnancy and lactation**

Pregnancy

There is no evidence as to drug safety in human pregnancy, nor is there evidence from animal work that it is free from hazard. 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 for 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.

**4.7 Effects on ability to drive and use machines**

Patients should be advised that, like all medicaments of this type, Nitrazepam Tablets may modify patients' performance at skilled tasks. Sedation, amnesia, impaired concentration and impaired muscle function may adversely affect the ability to drive or 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:

o The medicine has been prescribed to treat a medical or dental problem and

o You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and

o It was not affecting your ability to drive safely

**4.8 Undesirable effects**

Common adverse effects include drowsiness during the day, numbed emotions, reduced alertness, confusion, fatigue, headache, dizziness, muscle weakness, ataxia and double vision. These phenomena are dose related and occur predominantly at the start of therapy, they usually disappear with repeated administration. The elderly are particularly sensitive to the effects of centrally-depressant drugs.

The following undesirable effects have been divided into the following categories: 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 the available data)

| | |
|---|---|
| **Blood and the lymphatic system disorders**<br>Rare | <br>Blood dyscrasias |
| **Immune system disorders**<br>Very rare | <br>Hypersensitivity reactions (anaphylaxia and angiooedema) |
| **Psychiatric disorders**<br>Uncommon<br>Rare<br><br>Not known | <br>sleeping disorders, including insomnia.<br>Psychiatric and paradoxical reactions (4).<br>Muscular cramps, libido fluctuations<br>Dependence and abuse of benzo-diazepines, amnesia (2), depression (3), withdrawal symptoms (1) |
| **Nervous system disorders**<br>Common | <br>Dizziness, ataxia, drowsiness |

| | |
|---|---|
| Uncommon<br>Not known | tremor<br>Dysarthria |
| **Eye disorders**<br>Rare | Visual disturbances |
| **Ear and labyrinth disorders**<br>Rare | Vertigo |
| **Vascular disorders**<br>Rare | Hypotension |
| **Respiratory, thoracic and mediastinal disorders**<br>Rare | Respiratory depression |
| **Gastrointestinal disorders**<br>Rare | Nausea, gastrointestinal upsets |
| **Hepato-biliary disorders**<br>Rare | Jaundice |
| **Skin and subcutaneous tissue disorders**<br>Rare | Rash and other allergic skin reactionsStevens-Johnson syndrome |
| **Renal and urinary disorders**<br>Rare | Urinary retention |
| **Musculoskeletal, connective tissue and bone disorders**<br>Uncommon | Muscular weakness |

(1) Use (even at therapeutic doses) may lead to the development of physical and psychological dependence: discontinuation of the therapy may result in withdrawal or rebound phenomena, a transient syndrome whereby the symptoms that led to treatment with benzodiazepine or benzodiazepine-like agent recur in an enhanced form. It may be accompanied by other reactions including mood changes, anxiety and restlessness. Since the risk of withdrawal phenomena/rebound phenomena is greater after abrupt discontinuation of treatment, it is recommended that the dosage be decreased gradually.

(2) Anterograde amnesia may occur during the use of therapeutic doses since the risk is increased at higher doses. Amnesia may be combined with behavioural problems.

(3) Pre-existing depression may be revealed during the use of benzodiazepins.

(4) Reactions such as restlessness, excitation, irritability, aggressiveness, delusions, rage, nightmares, hallucinations, psychoses, inappropriate behaviour and other behavioural side effects may occur during benzodiazepine treatment. They can be very serious with this product. These side effects are observed more frequently in children and elderly patients.

Abuse of benzodiazepines has been reported.

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 overdosage 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:

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

Management:

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.

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.

### 5.2 Pharmacokinetic properties

*Absorption:*

The drug is well absorbed form the GI tract with peak blood levels being achieved within 2 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.

*Distribution:*

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.

*Biotransformation:*

Nitrazepam undergoes biotransformation to a number of metabolites, none of which possess significant clinical activity.

*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.

*Pharmacokinetic/ Pharmacodynamic relationship:*

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

### 5.3 Preclinical safety data

None stated.

## 6. Pharmaceutical particulars

### 6.1 List of excipients

lactose

magnesium stearate

maize starch

stearic acid

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years

### 6.4 Special precautions for storage

Do not store above 25°C. Store in the original package in order to protect from light and moisture.

### 6.5 Nature and contents of container

The product containers are rigid injection moulded polypropylene or injection blow-moulded polyethylene tablet containers with polyfoam wad and snap-on polyethylene lids; in case any supply difficulties should arise the alternative is amber glass bottles with screw caps and polyfoam wad or cotton wool.

The product may also be supplied in blister packs in cartons:

a) Carton: Printed carton manufactured from white folding box board.

b) Blister pack: (i) 250µm white rigid PVC. (ii) Surface printed 20µm hard temper aluminium foil with 5-7g/$M^2$ PVC and PVdC compatible heat seal lacquer on the reverse side.

Pack sizes: 28's, 30's, 56's, 60's, 84's, 90's, 100's, 112's, 168's, 180's, 250's, 500's, 1000's.

Product may also be supplied in bulk packs, for reassembly purposes only, in polybags contained in tins, skillets or polybuckets filled with suitable cushioning material. Bulk packs are included for *temporary* storage of the finished product before final packaging into the proposed marketing containers.

Maximum size of bulk packs: 25,000.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal and other handling

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

## 7. Marketing authorisation holder

Accord-UK Ltd

(Trading style: Accord)

Whiddon Valley

Barnstaple

Devon

EX32 8NS

## 8. Marketing authorisation number(s)

PL 0142/0086

## 9. Date of first authorisation/renewal of the authorisation

September 1977

September 1997

## 10. Date of revision of the text

07/02/2020

## Company Contact Details


Accord-UK Ltd

**Address**
Whiddon Valley, Barnstaple, Devon, EX32 8NS, UK

**WWW**
www.accord-healthcare.co.uk

**Telephone**
+44 (0)1271 385 200

**Fax**
+44 (0)1271 346 106

**Medical Information Direct Line**
+44 (0)1271 385 257

**Medical Information e-mail**
Medinfo@accord-healthcare.com