

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Nitrazepam Mixture 2.5mg/5ml Oral Suspension BP

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml contains 2.5 mg nitrazepam.

Excipient(s) with known effect:

Each 5 ml contains 2 g sucrose and 7.5 mg sodium.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Oral suspension.

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

Nitrazepam Mixture is a long acting benzodiazepine. 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 which can control the symptoms. The maximum dose should not be exceeded.

Duration of treatment: The duration of treatment should be as short as possible (see Posology) depending on the indication but should not exceed 4 weeks including any dose-tapering period for insomnia. Extension beyond this period should not take place without re-evaluation of the situation. 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 progressively decreased. Moreover, it is important that the patient should be aware of the possibility of rebound phenomena, thereby minimising anxiety over such symptoms should they occur while Nitrazepam mixture oral suspension is being discontinued.

Adults: 5 mg (10 ml) before retiring to bed. This dose may, if necessary, be increased to 10 mg (20 ml).

Elderly and patients with impaired liver and/or renal function:

2.5 mg (5 ml) before retiring to bed. This dose may, if necessary, be increased to 5 mg (10 ml).

If organic brain changes are present, the dosage should not exceed 5 mg 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 Mixture is contraindicated for use in children.

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

Oral administration.

To aid administration a 20 ml measuring cup with a range of graduations from 2.5 ml up to 20 ml is included in the package.

4.3 Contraindications

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.

The use of nitrazepam is also contraindicated in patients with the following:

Acute pulmonary insufficiency;

Respiratory depression;

Phobic or obsessional states;

Chronic psychosis;

Myasthenia gravis;

Sleep apnoea syndrome;

Severe hepatic insufficiency;

Acute porphyria;

Children.

Short-term treatment in children and juveniles

4.4 Special warnings and precautions for use

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 phobic or obsessional states, chronic psychosis or psychotic illness.

Benzodiazepines are not indicated to treat patients with severe hepatic insufficiency as they may precipitate encephalopathy.

A lower dose is also recommended for patients with chronic respiratory insufficiency due to the risk of respiratory depression (cross refer to section 4.3 – contraindicated in severe respiratory insufficiency).

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

Dependence and withdrawal: Use of benzodiazepines may lead to the development of physical and psychological dependence upon these products. The risk of dependence increases with dose and duration of treatment; it is also greater in patients

with a history of alcohol or drug abuse and 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/pain, 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. These symptoms, as well as a transient syndrome whereby the symptoms that led to treatment with a benzodiazepine recur in an enhanced form, may occur on withdrawal of treatment. It may be accompanied by other reactions including mood changes, anxiety or restlessness. Since the risk of withdrawal phenomena/rebound phenomena is greater after abrupt discontinuation of treatment, it is recommended that the dosage is decreased gradually.

In severe cases the following symptoms may occur: derealization, depersonalisation, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures.

In rare instances, withdrawal following excessive dosages may produce confusional states and psychotic manifestations and convulsions.

If a change is made to a benzodiazepine with a short duration of action, the patient should be warned that withdrawal symptoms may develop.

Abuse of benzodiazepines has been reported.

Amnesia: Benzodiazepines may induce anterograde amnesia. The condition occurs most often 1-2 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 7-8 hours (see also Undesirable Effects). If the patient is awoken during the period of maximum drug activity, recall may be impaired.

Psychiatric and paradoxical reactions: Extreme caution should be used when prescribing benzodiazepines to patients with personality disorders. Abnormal psychological reactions and rare behavioural effects like restlessness, agitation, excitement, confusion, irritability, paradoxical aggressive outbursts, delusion, rages, nightmares, hallucinations, psychoses, inappropriate behaviour and the uncovering of depression with suicidal tendencies are known to occur when using benzodiazepines. They may be quite severe and are more likely in children and the elderly. Should they occur, use of the medicinal product should be discontinued.

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).

Risk from concomitant use of opioids: Concomitant use of Nitrazepam Mixture 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 Mixture with opioids should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Nitrazepam Mixture 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).

Other specific 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 Posology, 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.

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

Benzodiazepines should not be used alone to treat depression or anxiety associated with depression (suicide may be precipitated in such patients).

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

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.

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

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

Excipients:

This medicinal product contains 2 g sucrose per 5 ml. This should be taken into account in patients with diabetes mellitus. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine. May be harmful to teeth.

This medicinal product contains 7.5 mg sodium per 5 ml, equivalent to 0.37% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Not recommended: Concomitant intake with alcohol. The sedative effect may be enhanced when the product is used in combination with alcohol. This affects the ability to drive or use machines.

Take into account:

Combination with Opioids: The concomitant use of sedative medicines such as benzodiazepines or related drugs such as Nitrazepam Mixture 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).

Combination with CNS depressants:

Enhancement of the central depressive effect may occur in cases of concomitant use with centrally-acting drugs such as barbiturates, antipsychotics (neuroleptics), tranquillisers, hypnotics, anxiolytics/sedatives, antidepressant agents, analgesics and anaesthetics, anti-epileptic products and 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 requires special supervision.

When nitrazepam is used in conjunction with anti-epileptics, side effects and toxicity may be more evident for drugs containing barbiturates, carbamazepine and hydantoin, or their combinations. This requires extra care in adjusting dosage in the initial stages of treatment.

Phenytoin concentration may be increased or decreased.

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. To a lesser degree this also applies to benzodiazepines that are metabolised only by conjugation.

Known inducers of hepatic enzymes (e.g. rifampicin) may reduce the half-life of nitrazepam and increase the clearance.

Benzodiazepines possibly antagonise the effects of levodopa.

Probenecid may increase the sedative effects, possibly excessively.

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

Fertility

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

Pregnancy

Nitrazepam crosses the placental barrier. The feto-maternal 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.

If, for compelling medical reasons, the product is administered during the last trimester of pregnancy or during labour, effects on the neonate, such as irregularities in the foetal heart rate, hypothermia, hypotonia, poor sucking and moderate respiratory depression, can be expected, due to the pharmacological action of the compound.

Moreover, infants born to mothers who took benzodiazepines chronically during 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, benzodiazepines should not be given to breast feeding mothers.

4.7 Effects on ability to drive and use machines

Patients should be advised that Nitrazepam Mixture may modify their performance at skilled tasks. Sedation, amnesia, impaired concentration and impaired muscular function may adversely affect the ability to drive or to use machines. If insufficient sleep duration occurs, the likelihood of impaired alertness may be increased (See also Interactions). Patients should further be advised that alcohol may intensify any impairment and should 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

The following commonly occur predominantly at the start of therapy and usually disappear with repeated administration:

ataxia or double vision, confusion, dizziness, drowsiness, fatigue, headache, muscle weakness, numbed emotions, reduced alertness.

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

Undesirable effects may persist into the following day due to the long half-life.

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 1/1,000 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, confusional state, depression (pre-existing depression may be unmasked).

Rare: Libido disorder

Frequency not known: 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

Frequency 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 at: 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 Mixture 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, symptoms may 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. It 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. If CNS depression is severe consider the use of flumazenil (Anexate) a benzodiazepine antagonist. This is a specific IV antidote for use in emergency situations and should rarely be required. It has a short half-life (about an hour) and should NOT BE USED IN MIXED OVERDOSE OR AS A “DIAGNOSTIC” TEST. It is contraindicated in patients with epilepsy who have been treated with benzodiazepines and in the presence of drugs that reduce seizure threshold (e.g. tricyclic antidepressants). 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 long acting benzodiazepine with anxiolytic, sedative and hypnotic characteristics.

5.2 Pharmacokinetic properties

Absorption

Nitrazepam mixture Oral suspension is well absorbed from the GI tract with peak blood levels of nitrazepam being achieved within 2-3 hours of administration.

Half-life is approximately 30 hours and plasma steady state levels are achieved after 5 days.

Elimination

Nitrazepam is metabolised in the liver with the excretion mainly in the urine in the form of metabolites and up to about 20% of an oral dose being found in faeces.

Biotransformation

Nitrazepam undergoes biotransformation to a number of metabolites, none of which possess significant clinical activity. About 5% is excreted unchanged in the urine together with less than 10% each of the 7-amino- and 7 acetylamino-metabolites in the first 48 hours. The percentage ratio between the CSF (cerebrospinal fluid) and the plasma concentration increases from 8% at 2 hours to 16% at 36 hours after administration. Nitrazepam is eliminated very slowly from the CSF with a half-life approximately 2 times longer than that of plasma (about 27 hours in plasma and 68 hours in CSF) corresponding partially to the unbound fraction of plasma protein.

5.3 Preclinical safety data

Preclinical studies provide only limited evidence of safety. Nitrazepam has no significant systemic toxicity potential at the doses in clinical use with the exception of use in pregnancy and lactation for which evidence of safety is lacking.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose

Microcrystalline cellulose

Carboxymethyl cellulose sodium

Mixed esters of p-hydroxybenzoic acid

Cherry flavour

Water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C). Protect from light. Do not freeze.

6.5 Nature and contents of container

Amber glass bottles (Type III) containing 70 ml of suspension with a tamper-evident child-resistant polypropylene (PP) cap with a polyethylene (PE) liner and a 20 ml measuring cup (polypropylene) with increments in the range of 2.5 ml to 20 ml.

6.6 Special precautions for disposal

The bottle should be shaken before use.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 00427/0288

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