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 2.5mg nitrazepam.

Excipient(s) with known effect:
Each 5ml contains
2g sucrose
7.5mg sodium
3.5mg methyl-parahydroxybenzoate
1mg ethyl parahydroxybenzoate
0.5mg propyl parahydroxybenzoate

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.

Prior to starting treatment with nitrazepam, a discussion should be held with patients to put in place a strategy for ending treatment with nitrazepam in order to minimise the risk of dependence, addiction and drug withdrawal syndrome (see section 4.4). Treatment should be given for the shortest possible duration.

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.

Drug dependence, tolerance and potential for abuse

Drug addiction comprises behavioural, cognitive and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use and

possible tolerance or physical dependence. Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, which manifests as withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug. Addiction and dependence are related but distinct presentations and in discussing these themes, terminology that apportion blame to the individual should be avoided.

For all patients, prolonged use of this product may lead to drug dependence and addiction but can occur with short-term use at recommended therapeutic doses. The risks are increased in individuals with current or past history of substance misuse disorder (including alcohol misuse) or mental health disorder (e.g., major depression).

Additional support and monitoring may be necessary when prescribing for patients at risk of drug misuse.

A comprehensive patient history should be taken to document concomitant medications, including over-the-counter medicines and medicines obtained on-line, and past and present medical and psychiatric conditions.

Patients may find that treatment is less effective with chronic use and express a need to increase the dose to obtain the same level of symptom control as initially experienced. Patients may also supplement their treatment with additional medications to achieve the same effect. These could be signs that the patient is developing tolerance. The risks of developing tolerance should be explained to the patient.

Overuse or misuse may result in overdose and/or death. It is important that patients only use medicines that are prescribed for them at the dose they have been prescribed and do not give this medicine to anyone else.

Patients should be closely monitored for signs of misuse, abuse, or addiction.

The clinical need for treatment with nitrazepam should be reviewed regularly, with frequent assessments of patients being undertaken during the course of their treatment.

Drug withdrawal syndrome

Prior to starting treatment with nitrazepam, a discussion should be held with patients to explain the risk of dependence, addiction, and drug withdrawal syndrome. A withdrawal strategy for ending treatment with nitrazepam should also be put in place with the patient before starting treatment (there may be exceptions to this in specific clinical situations such as symptom management in end of life palliative care).

Drug withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. When a patient no longer requires therapy, it is advisable to taper the dose gradually to minimise symptoms of withdrawal. Tapering from a high dose may take in excess of weeks or months. Patients should be informed of this when the medication is first prescribed.

The reduction schedule for a patient should be tailored to the individual and should be modified to allow intolerable withdrawal symptoms to improve before making the next reduction. If using a published withdrawal schedule, apply it flexibly to accommodate the person's preferences, changes to their circumstances and the response to dose reductions.

Suggest a slow stepwise rate of reduction proportionate to the existing dose, so that decrements become smaller as the dose is lowered, unless clinical risk is such that rapid withdrawal is needed.

If a patient develops withdrawal reactions, consider pausing the taper or increasing the dosage to the previous tapered dosage level.
If women take this drug during pregnancy, there is a risk that their newborn infants will experience neonatal withdrawal syndrome.

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

This medicinal product contains parabens: 3.5mg methyl parahydroxybenzoate, 1mg ethyl parahydroxybenzoate and 0.5mg propyl parahydroxybenzoate per 5ml. The parabens may cause allergic reactions (possibly delayed).

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 hydantoins, 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, some azole 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 increases 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, drug abuse, drug dependence (see section 4.4), agitation, aggression, delusion, anger, nightmare, hallucination, psychotic disorder.

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, drug withdrawal symptoms (see section 4.4, Special warnings and precautions).

Symptoms reported following discontinuation of benzodiazepines include headaches, muscle pain, anxiety, tension, depression, insomnia, restlessness, confusion, irritability, sweating, and the occurrence of “rebound” phenomena whereby the symptoms that led to treatment with benzodiazepines recur in an enhanced form. These symptoms may be difficult to distinguish from the original symptoms for which the drug was prescribed.

In severe cases the following symptoms may occur: derealisation; depersonalisation; hyperacusis; tinnitus; numbness and tingling of the extremities; hypersensitivity to light, noise, and physical contact; involuntary movements; hyperreflexia, tremor, nausea, vomiting; diarrhoea, abdominal cramps, loss of appetite, agitation, palpitations, tachycardia, panic attacks, vertigo, short-term memory loss, hallucinations/delirium; catatonia; hyperthermia, convulsions. Convulsions may be

more common in patients with pre-existing seizure disorders or who are taking other drugs that lower the convulsive threshold such as antidepressants.

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
Patients should be informed of the signs and symptoms of overdose and to ensure that family and friends are also aware of these signs and to seek immediate medical help if they occur.

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 acetylaminometabolites 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.

6.1 List of excipients

Sucrose
Microcrystalline cellulose
Carboxymethyl cellulose sodium
Methyl parahydroxybenzoate
Ethyl parahydroxybenzoate
Propyl parahydroxybenzoate
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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