SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Mogadon 5 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg of Nitrazepam.

There is 301 mg lactose monohydrate per tablet.
For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablets

Round, white tablets with “ V ”
MOG 5
imprinted on one face with a single break bar on the other.

The tablet can be divided into equal doses.

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.

4.2 Posology and method of administration

Posology:

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 Mogadon. Doses should not exceed half those normally recommended.
If organic brain changes are present, the dosage of Mogadon 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

Mogadon tablets are contraindicated for use in children.

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

Mogadon 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 hypotension 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, 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

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.

Concomitant use of Mogadon 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 Mogadon with opioids should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Mogadon 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.

<u>Drug dependence, tolerance and potential for abuse</u>

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.

<u>Drug withdrawal syndrome</u>

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.

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.

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 or CNS toxicity with age has been observed, especially at high doses. Therefore the dosage of Mogadon 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.

Lactose
Patients with rare hereditary problems of galactose intolerance, the 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 barbiturates, antipsychotics, tranquillisers, antidepressants, hypnotics, anxiolytics, analgesics and anaesthetics, anticonvulsants and sedative antihistamines, antihypertensives and beta-blockers.

The concomitant use of sedative medicines such as benzodiazepines or related drugs such as Mogadon 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).

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.

When Mogadon is used in conjunction with anticonvulsant 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, 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.

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

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.
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 Mogadon 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, Mogadon 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:
  - 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.

Drug dependence (see section 4.4)

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, enterograde, 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 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 Mogadon 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 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 (consult separate product information prior to use).

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.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Hypnotics and Sedatives, Benzodiazepine derivatives,

ATC Code: N05CD02

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

Mogadon 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. $GABA_A$ receptors may become less responsive to the continuing acute effects of benzodiazepines, either as a result of adaptation in the $GABA_A$ 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 Mogadon 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 Mogadon, 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:
The drug is well absorbed form the GI tract with peak blood levels being achieved within 2 hours of administration. 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 inductor nor an inhibitor of metabolic enzymes.

Elimination:
The half-life of nitrazepam in plasma on average is 30 hours. In the cerebrospinal fluid the half-life is about 70 hours. In elderly patients the plasma elimination half-life rises to 40 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 Mogadon 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 dose-related 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

Each 5 mg tablet contains the following excipients: lactose, starch maize white and magnesium stearate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

HDPE or glass bottles: 5 years.

PVC/Aluminium blisters: 5 years.

Clic-loc containers and polypropylene mini kegs: 2 years.

6.4 Special precautions for storage

The recommended maximum storage temperature for Mogadon tablets is 25°C.

All packs should be protected from light and the blister packs should be protected from moisture i.e. stored in a dry place.

6.5 Nature and contents of container

HDPE or glass bottles, in packs of 30 or 100.

PVC/Aluminium blister packs, containing 30 or 50 tablets.

Clic-loc containers, in a pack of 10.

Polypropylene mini-kegs, containing 5000 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused product should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Viatris Products Limited,
Station Close,
Potters Bar,
EN6 1TL,
United Kingdom.

8 MARKETING AUTHORISATION NUMBER

PL 46302/0135

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

3 May 1999

10 DATE OF REVISION OF THE TEXT

11/02/2026