SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Diazepam 10 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg diazepam.

Excipient(s) with known effect
Each 10 mg tablet contains 130.86 mg of lactose

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Flat, blue tablets with bevelled edges, 8 mm diameter. One face embossed with “DZ” and “10” separated by a breakline. The reverse face is plain.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults
Benzodiazepines, including diazepam, are indicated for the short-term relief (up to 4 weeks only) of anxiety that is severe, disabling or subjecting the individual to unacceptable distress, occurring alone or in association with insomnia or short-term psychosomatic, organic or psychotic illness.
Cerebral palsy.
Muscle spasm.
As an adjunct to certain types of epilepsy (eg myoclonus).
Symptomatic treatment of acute alcohol withdrawal.
As oral premedication for the nervous dental patient.
For premedication before surgery.

Children
Control of tension and irritability in cerebral spasticity in selected cases.
As an adjunct to the control of muscle spasm in tetanus.
Oral premedication (see section 4.4).

4.2 Posology and method of administration

Recommended dose and dosage schedule: As directed by a physician.

Posology
As an anxiolytic, the lowest dose which can control symptoms should be used. It should not be continued beyond 4 weeks. Long-term chronic use is not recommended. Treatment should always be tapered off gradually. Patients who have taken benzodiazepines for a long time may require a longer period during which doses are reduced.

Adults
Anxiety states, obsessive-compulsive neuroses, and other psychiatric disorders: 5 – 30 mg daily in divided doses.
Alcohol withdrawal: 5-20 mg, repeated if necessary in 2-4 hours.
Insomnia associated with anxiety: 5-15 mg before bedtime.
Cerebral palsy: 5-60mg daily in divided doses.
Upper motor neuronic spasticity: 5-60mg daily in divided doses.
Muscle spasm of varied aetiology, fibrositis, cervical spondylosis: 5-15mg daily in divided doses.
Adjunct to the management of some types of epilepsy: 2-60 mg daily in divided doses.
Oral premedication in dental patients: 5mg the night before, 5mg on waking and 5mg two hours before the appointment.
Oral Premedication before surgery: 5mg-20mg.

Children
Alternative presentations of diazepam are recommended for paediatric usage in order to obtain suitable doses of less than 5mg.
Spastic children with minimal brain damage: 5-40mg daily in divided doses.
Oral Premedication before surgery (see section 4.4): 2mg-10mg

Elderly and debilitated patients
Doses should be half the above recommended doses.

Renal and hepatic impairment (see section 4.4)
The use of diazepam in hepatic impairment may precipitate coma, therefore the dose should be reduced or an alternative drug considered. In severe renal impairment the dose should be reduced.

Method of Administration
For oral administration.

4.3 Contraindications

- Hypersensitivity to the active substance, other benzodiazepines or to any of the excipients listed in section 6.1
- Phobic or obsessional states; chronic psychosis, hyperkinesis (paradoxical reactions may occur).
- Acute pulmonary insufficiency; respiratory depression, acute or chronic severe respiratory insufficiency (ventilatory failure may be exacerbated)
- Myasthenia gravis (condition may be exacerbated).
- Sleep apnoea (condition may be exacerbated).
- Severe hepatic insufficiency (elimination half-life of diazepam may be prolonged).
- Acute porphyria.
- Diazepam should not be used as monotherapy in patients with depression or those with anxiety and depression as suicide may be precipitated in such patients.
- Planning a pregnancy (see section 4.6).
- Pregnancy (unless there are compelling reasons - see section 4.6).

4.4 Special warnings and precautions for use

- The concomitant use of diazepam with alcohol and/or CNS depressants should be avoided. Such concomitant use has the potential to increase the clinical effects of diazepam possibly including severe sedation, clinically relevant respiratory and/or cardio-vascular depression (see section 4.5).

- *Duration of Treatment* - The duration of treatment should be as short as possible depending on the indication,-. The patient must be evaluated after a period of no more than 4 weeks and then regularly thereafter in order to assess the need for continued treatment, especially if the patient is free of symptoms. In general, treatment must not last any longer than 8-12 weeks, including the tapering off process. Extension beyond these periods 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 minimizing anxiety over such symptoms should they occur while diazepam is being discontinued. There are indications that, in the case of benzodiazepines with a short duration of action, withdrawal phenomena can become manifest within the dosage interval, especially when the dosage is high.

- 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.

- *Dependence and Withdrawal* - Withdrawal symptoms occur with benzodiazepines following normal therapeutic doses given for short periods of time.
  Use of diazepam may lead to the development of physical and psychic dependence. The risk of dependence increases with the dose and duration of treatment, and in patients with a history of alcoholism and 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.
Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms (see Section 4.8 Undesirable Effects). These may consist of headaches, muscle pain, extreme anxiety, tension, restlessness, confusion and irritability. In severe cases the following symptoms may occur: derealisation, depersonalisation, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures.
Rebound insomnia and anxiety: a transient syndrome whereby the symptoms that led to treatment with diazepam may recur in an enhanced form on withdrawal of treatment. It may be accompanied by other reactions including mood changes, anxiety or sleep disturbances and 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.
As sudden discontinuation of benzodiazepines may result in convulsions, particular care should be taken in patients with epilepsy, other patients who have had a history of seizures or in alcohol or drug dependants.

- *Tolerance* - Limits of tolerance in patients with organic cerebral changes (particularly arteriosclerosis) or cardio-respiratory insufficiency may be very wide; care must be taken in adapting the dosage with such patients. Some loss of efficacy to the hypnotic effects of diazepam may develop after repeated use for a few weeks.

- Alcohol should be avoided during treatment with diazepam (additive CNS depression).

- Amnesia - diazepam may induce anterograde amnesia. The condition occurs most often several hours after ingesting the product and therefore to reduce the risk patients should ensure that they will be able to have uninterrupted sleep of 7-8 hours. Anterograde amnesia may occur using therapeutic doses, the risk increases with higher doses.

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

- Diazepam should be used with caution in patients with a history of alcohol or drug abuse as these are patients predisposed to habituation and dependence.

- Hypo-albuminaemia may predispose patient to higher incidence of sedative side effects.

- Extreme caution should be used in prescribing diazepam to patients with personality disorders.

- Benzodiazepines should not be used in patients with severe hepatic insufficiency as they may precipitate encephalopathy. In patients with chronic hepatic disease dosage may need to be reduced.

- Cerebral sensitivity is increased in severe renal failure; therefore lower doses should be used (see section 4.2)

- Hypnotics should be avoided in the elderly who are at risk of becoming ataxic and confused and so liable to fall and injure themselves. If, based on clinical need, a decision to treat is nevertheless taken; treatment should be initiated at a lower dose (see section 4.2).

- Caution should be exercised when using diazepam peri-operatively in children, as effects and timing of response may be unreliable and paradoxical effects may occur.

Risk from concomitant use of opioids:

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

<u>Psychiatric and 'paradoxical' reactions</u>

- Paradoxical reactions like restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects are known to occur when using benzodiazepines. Should this occur, use of the drug should be discontinued. They are more likely to occur in children and the elderly.

Paediatric Population

- Benzodiazepines should not be given to children without careful assessment of the need to do so; the duration of treatment must be kept to a minimum. Safety and effectiveness of diazepam in paediatric patients below the age of 6 months have not been established.

Special Populations

- Elderly and debilitated patients should be given a reduced dose (see section 4.2). Due to the myorelaxant effect there is a risk of falls and consequently hip fractures in the elderly.
- A lower dose is also recommended for patients with chronic respiratory insufficiency due to the risk of respiratory depression.
- The usual precautions in treating patients with impaired renal function should be observed. In renal failure, the half-life of diazepam is not clinically significantly changed, and dose adjustment is usually not necessary.
- 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).

- Potentially suicidal individuals should not have access to large amounts of diazepam due to the risk of overdosing.

- Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Not recommended

Alcohol

Diazepam should not be used together with alcohol (CNS inhibition enhanced sedative effects: impaired ability to drive/ operate machinery).

Sodium oxybate

Avoid concomitant use (enhanced effects of sodium oxybate).

HIV-protease inhibitors

Avoid concomitant use (increased risk of prolonged sedation) – see below for zidovudine.

Take into account

Pharmacodynamic interactions

If diazepam is used with other centrally acting agents, careful consideration has to be given to the pharmacology of the agents employed, particularly with compounds that may potentiate or be potentiated by the action of diazepam, such as neuroleptics, anxiolytics/sedatives, hypnotics, antidepressants, anticonvulsants, sedating antihistamines, antipsychotics, anaesthetics for general anaesthesia and narcotic analgesics. Such concomitant use may increase sedative effects and cause depression of respiratory and cardiovascular functions. Concomitant use of narcotic analgesics may promote psychic dependency due to enhancement of euphorigenic effects.

Antiepileptic drugs

Pharmacokinetic studies on potential interactions between diazepam and antiepileptic drugs have produced conflicting results. Both depression and elevation of drug levels, as well as no change, have been reported. Phenobarbital taken concomitantly may result in an additive CNS effect.

Increased risk of sedation and respiratory depression. Phenobarbital is a known inducer of CYP3A4 and increases hepatic metabolism of diazepam. Reduced effect of diazepam.

Therefore, special care should be taken in adjusting the dose in the initial stages of treatment.

Side effects may be more evident with hydantoins or barbiturates.

Diazepam has been reported to be displaced from protein-binding sites by sodium valproate (increased serum levels: increased risk of drowsiness).

Narcotic analgesics

Enhancement of the euphoria may lead to increased psychological dependence.

Other drugs enhancing the sedative effect of diazepam
*C*isapride, lofexidine, nabilone, disulfiram and the muscle-relaxants – baclofen, Tizanidine, suxamethonium and tubocurarin.

Opioids:
The concomitant use of sedative medicines such as benzodiazepines or related drugs such as Diazepam 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).

Compounds that affect hepatic enzymes (particularly cytochrome P450)
Inhibitors (eg cimetidine: isoniazid: erythromycin: omeprazole: esomeprazole) reduce clearance and may potentiate the action of benzodiazepines.
Itraconazloe, ketoconazole, and to a lesser extent fluconazole and voriconazole are potent inhibitors of the cytochrome P450 isoenzyme CYP3A4 and may increase plasma levels of benzodiapines. The effects of benzodiapines may be increased and prolonged by concomitant use. A dose reduction of the benzodiazepine may be required.

Rifamycins (rifampicin)
Rifampicin is a potent inducer of CYP3A4 and substantially increases the hepatic metabolism and clearance of diazepam. In a study with healthy subjects administered 600 mg or 1.2 g rifampicin daily for 7 days, the clearance of diazepam was increased by about fourfold. Co-administration with rifampicin gives rise to substantially decreased concentrations of diazepam. Reduced effect of diazepam. The concomitant use of rifampicin and diazepam should be avoided.

Antihypertensives, vasodilators & diuretics
Enhanced hypotensive effect with ACE inhibitors, alpha-blockers, angiotensin–II receptor antagonists, calcium channel blockers, adrenergic neurone blockers, beta-blockers, moxonidine, nitrates, hydralazine, minoxidil, sodium nitroprusside and diuretics. Enhanced sedative effect with alpha-blockers or moxonidine.

Dopaminergics
Possible antagonism of the effect of levodopa.

Antacids
Concurrent use may delay absorption of diazepam

Antiviral agents (atazanavir, ritonavir, delavirdine, efavirenz, indinavir, nelfinavir, saquinavir)
Antiviral agents may inhibit the CYP3A4 metabolic pathway for diazepam. Increased risk of sedation and respiratory depression. Therefore, concomitant use should be avoided.

Zidovudine
Increased zidovudine clearance by diazepam.

Oral contraceptives
Inhibition of oxidative metabolism of diazepam. Increased effects of diazepam.
Co-administration of diazepam and combined oral contraceptives has been known to cause breakthrough bleeding. The mechanism of this reaction is unknown. Breakthrough bleeding, but no contraceptive failures have been reported.

Theophylline
A proposed mechanism is competitive binding of theophylline to adenosine receptors in the brain. Counteraction of the pharmacodynamic effects of diazepam, e.g. reduction of sedation and psychomotor effects.

Caffeine
Concurrent use may result in reduced sedative and anxiolytic effects of diazepam.

Grapefruit juice
Inhibition of CYP3A4 may increase the plasma concentration of diazepam (possible increased sedation and amnesia). C_{max} is increased by 1.5 times and AUC by 3.2 times. Possible increased effect of diazepam.
This interaction may have little significance in healthy individuals, but it is not clear is if other factors such as old age or liver cirrhosis increase the risk of adverse effects with concurrent use.

Clozapine
Mechanism: Pharmacodynamic synergism.
Effect: Severe hypotension, respiratory depression, unconsciousness and potentially fatal respiratory and/or cardiac arrest. Therefore, concomitant use is not recommended and should be avoided.

Pharmacokinetic interactions

Diazepam is mainly metabolised to the pharmacologically active metabolites N-desmethyldiazepam, temazepam and oxazepam. The oxidative metabolism of diazepam is mediated by CYP3A4 and CYP2C19 isoenzymes. Oxazepam and temazepam are further conjugated to glucuronic acid. Inhibitors of CYP3A4 and/or CYP2C19 can give rise to increased concentrations of diazepam while enzyme inducing drugs such as rifampicin, hypericum perforatum and certain antiepileptics can result in substantially decreased plasma concentrations of diazepam.

Carbamazepine
Carbamazepine is a known inducer of CYP3A4 and increases hepatic metabolism of diazepam. This can result in up to three-fold greater plasma clearance and a shorter half-life of diazepam. Reduced effect of diazepam.

Phenytoin
Phenytoin is a known inducer of CYP3A4 and increases hepatic metabolism of diazepam. Reduced effect of diazepam.
The metabolism of phenytoin may be increased or decreased or remain unaltered by diazepam in an unpredictable way. Increased or decreased serum concentration of phenytoin. Phenytoin concentrations should be monitored more closely when diazepam is added or discontinued.

Azoles (fluconazole, itraconazole, ketoconazole, voriconazole)
Increased plasma concentration of benzodiazepines, due to inhibition of the CYP3A4 and/or CYP2C19 metabolic pathway.

Co-administration with 400 mg fluconazole on the first day and 200 mg on the second day increased the AUC of a single 5 mg oral dose of diazepam 2.5-fold and prolonged the half-life from 31 hours to 73 hours.

Voriconazole
A study with healthy subjects found that 400 mg voriconazole twice daily on the first day and 200 mg twice daily on the second day increased the AUC of a single 5 mg oral dose of diazepam 2.2-fold and prolonged the half-life from 31 hours to 61 hours.
Increased risk of undesired effects and toxicity of benzodiazepine. Concomitant use should be avoided or the dose of diazepam reduced.

Fluvoxamine
Fluvoxamine inhibits both CYP3A4 and CYP2C19 which leads to inhibition of the oxidative metabolism of diazepam. Co-administration with fluvoxamine results in an increased half-life and an approximately 190% increased plasma concentrations (AUC) of diazepam. Drowsiness, reduced psychomotor performance and memory. Preferably, benzodiazepines that are metabolised via a non-oxidative pathway should be used instead.

Corticosteroids
Chronic use of corticosteroids may cause increased metabolism of diazepam due to induction of cytochrome P450 isoenzyme CYP3A4, or of enzymes responsible for glucuronidation. Reduced effects of diazepam.

Cimetidine
Cimetidine inhibits the hepatic metabolism of diazepam, reducing its clearance and prolonging its half-life. In one study where 300 mg cimetidine was administered four times daily for 2 weeks, the combined plasma level of diazepam and its active metabolite, desmethyldiazepam, was found to be increased by 57%, but reaction times and other motor and intellectual tests remained unaffected. Increased action of diazepam and increased risk of drowsiness. Reduction of the diazepam dose may be necessary.

Omeprazole
Omeprazole inhibits the CYP2C19 metabolic pathway for diazepam. Omeprazole prolongs the elimination half-life of diazepam and increases the plasma concentrations (AUC) of diazepam approximately between 30% - 120%. The effect is seen in CYP2C19 extensive metabolisers but not in slow metabolisers, with a low clearance of diazepam. Increased action of diazepam. Reduction of the diazepam dose may be necessary.

Esomeprazole
Esomeprazole inhibits the CYP2C19 metabolic pathway for diazepam. Co-administration with esomeprazole results in an extended half-life and an increase in

plasma concentrations (AUC) of diazepam by approximately 80%. Increased effect of diazepam. Reduction of the diazepam dose may be necessary.

Isoniazid
Isoniazid inhibits the CYP2C19 and CYP3A4 metabolic pathway for diazepam. Co-administration with 90 mg isoniazid twice daily for 3 days resulted in a prolonged elimination half-life of diazepam and in a 35% increased plasma concentration (AUC) of diazepam. Increased effect of diazepam.

Itraconazole
Increased plasma concentration of diazepam due to inhibition of the CYP3A4 metabolic pathway. In a study with healthy subject given 200 mg itraconazole daily for 4 days increased the AUC of a single 5 mg oral dose of diazepam by about 15%, but there was no clinically significant interaction as determined by psychomotor performance tests. Possible increased effect of diazepam.

Fluoxetine
Fluoxetine inhibits the metabolism of diazepam via CYP2C19 and other pathways, resulting in elevated plasma concentrations and decreased clearance of diazepam. Increased effect of diazepam. Concomitant use should be monitored closely.

Disulfiram
Reduced metabolism of diazepam leading to prolonged half-life and increased plasma concentration of diazepam. The elimination of the N-desmethyl metabolites of diazepam is slowed down which can give rise to marked sedative effects. Increased risk of CNS inhibition such as sedation.

Cisapride
Accelerated absorption of diazepam. Temporary increase of the sedative effects of orally administered diazepam.

Levodopa
Concomitant use with diazepam resulted in reduced effects of levodopa in a small number of case reports.

Ketamine
Due to similar oxidative processes, diazepam competitively inhibits ketamin metabolism. Pre-medication with diazepam leads to prolonged half-life of ketamine with enhanced effect as a result. Increased sedation.

4.6 Fertility, pregnancy and lactation

The safety of diazepam in human pregnancy has not been established. It should not be used in the first and third trimesters. There may be a small increase in the risk of congenital malformation, particularly oral cleft, with the use of benzodiazepines in the first trimester. However, a causal relationship has not been established.

If the product is prescribed to a woman of child-bearing 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.

Pregnancy
If, for compelling medical reasons, the product is administered during the late phase of pregnancy, or during labour at high doses, effects on the neonate, such as hypothermia, hypotonia ("Floppy Infant Syndrome"), irregularities in the heart rate, poor suckling and moderate respiratory depression, can be expected due to the pharmacological actions of the compound.

Moreover, infants born to mothers who took benzodiazepines chronically during the latter stages of pregnancy may have developed physical dependency and may be at some risk of developing withdrawal symptoms in the postnatal period.
Studies in animals have shown reproductive toxicity (see section 5.3).

Lactation
Benzodiazepines are found in breast milk. Reports have demonstrated that milk:plasma concentration ratios vary between 0.2 and 2.7. There is therefore a risk of accumulation in the breast-feeding child. Benzodiazepines should not be given to breast-feeding mothers.

Fertility
Studies in animals have shown a decrease in pregnancy rate and reduced number of surviving offspring in rats at high doses. There are no human data.

4.7 Effects on ability to drive and use machines

Sedation, amnesia and impaired muscular function may adversely affect the ability to drive or use machines. If insufficient sleep occurs, the likelihood of impaired alertness may be increased (see also interactions).
Impaired function and sedation may occur the following morning and for several days after.
Patients should be warned that effects on the central nervous system may persist into the day after administration even after a single dose.

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

Drowsiness, numbed emotions, reduced alertness, confusion, fatigue, headache, dizziness, muscle weakness, ataxia or double vision predominantly occur at the start of therapy but usually disappear with repeated administration. Among elderly patients there may be confusion conditions at high dose levels. There is an increased risk of falls and associated fractures in elderly patients using benzodiazepines. Increased salivary and bronchial secretion has been reported, in particular in children.

Amnesia
Anterograde amnesia may occur using therapeutic dosages, the risk increasing at higher dosages. Amnestic effects may be associated with inappropriate behaviour (see section 4.4).

Dependence
Chronic use (even at therapeutic doses) may lead to the development of physical and psychic dependence: discontinuation of the therapy may result in withdrawal or rebound phenomena (see section 4.4). Abuse of benzodiazepines has been reported.

The frequencies of adverse events are ranked according to the following:
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).

System Organ Class	**Frequency**	**Undesirable effects**
Blood and lymphatic system disorders	Rare	Blood dyscrasias
	Very rare	Leukopenia
Immune system disorders	Very rare	Anaphylaxis.
Psychiatric disorders	Common	Confusion.
	Rare	Psychiatric and paradoxical reactions such as excitation, restlessness, agitation, irritability, aggressiveness, delusion, rages, hallucinations, psychoses, memory loss, nightmares, inappropriate behaviour and other adverse behavioural effects.[a] Emotional poverty, decreased alertness and depression.[b]

Nervous system disorders	Very common	Drowsiness.
	Common	Ataxia, impaired motor ability, tremor.
	Uncommon	Anterograde amnesia.[c] Concentration difficulties, balance disorders, dizziness, headache, slurred speech.
	Rare	Unconsciousness, insomnia, dysarthria.
Eye disorders	Not known	Reversible disorders of vision: blurred vision, diplopia, nystagmus.
Cardiac disorders	Rare	Bradycardia, heart failure including cardiac arrest.
Vascular disorders	Rare	Hypotension, syncope.
Respiratory, thoracic and mediastinal disorders	Uncommon	Respiratory depression.
	Rare	Respiratory arrest, increased bronchial secretion.
	Not Known	Apnoea
Gastrointestinal disorders	Uncommon	Gastrointestinal disorders (nausea, vomiting, constipation, diarrhoea), increased salivary secretion.
	Rare	Dry mouth, increased appetite.
Hepatobiliary disorders	Rare	Jaundice, changes of hepatic parameters (elevation of ALT, AST, alkaline phosphatase).
Skin and subcutaneous tissue disorders	Uncommon	Allergic skin reactions (itching, erythema, rash).
Musculoskeletal and connective tissue disorders	Uncommon	Myasthenia.
Renal and urinary disorders	Rare	Urinary retention, incontinence.
Reproductive system and breast disorders	Rare	Gynaecomastia, impotence, increased or reduced libido.
General disorders and administration site conditions	Common	Fatigue, withdrawal symptoms (anxiety, panic, palpitations, sweating, tremor, gastrointestinal disorders, irritability, aggression, disrupted sensory perception, muscle spasms, general malaise, loss of appetite, paranoid psychosis, delirium and epileptic attacks).[d]
	Not known	Anaphylaxis
Investigations	Very rare	Elevation of transaminases.

[a] Known to occur when using benzodiazepines or benzodiazepine-like agents. These reactions may be quite severe. They are more likely to occur in children and the elderly. Diazepam should be discontinued if such symptoms occur (see section 4.4).
[b] Pre-existing depression may be unmasked during benzodiazepine use.
[c] May occur using therapeutic dosages, the risk increasing at higher dosages. Amnestic effects may be associated with inappropriate behaviour (see section 4.4).

[d] The likelihood and degree of severity of withdrawal symptoms is dependent on the duration of treatment, dose level and degree of dependency.

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

Features
The symptoms of diazepam overdose are mainly an intensification of the therapeutic effects (ataxia, drowsiness, dysarthria, sedation, muscle weakness, profound sleep, hypotension, bradycardia, nystagmus) or paradoxical excitation. In most cases only observation of vital functions is required.
Extreme overdosage may lead to coma, areflexia, cardiorespiratory depression and apnoea, requiring appropriate countermeasures (ventilation, cardiovascular support). Benzodiazepine respiratory depressant effects are more serious in patients with severe chronic obstructive airways disease. Severe effects in overdose also include rhabdomyolysis and hypothermia.

Management
Maintain a clear airway and adequate ventilation.
Consider activated charcoal (50 g for an adult, 1 g/kg for a child) in adults who have taken more than 100 mg or children who have taken more than 1 mg/kg within 1 hour, provided they are not too drowsy.
Monitoring level of consciousness, respiratory rate, pulse oximetry and blood pressure in symptomatic patients.
Consider arterial blood gas analysis in patients who have a reduced level of consciousness (GCS < 8; AVPU scale P or U) or have reduced oxygen saturations on pulse oximetry.
Correct hypotension by raising the foot of the bed and by giving an appropriate fluid challenge. Where hypotension is thought mainly due to decreased systemic vascular resistance, drugs with alpha-adrenergic activity such as noradrenaline or high dose dopamine (10-30 micrograms/kg/min) may be beneficial. The dose of inotrope should be titrated against blood pressure.
If severe hypotension persists despite the above measures, then central venous pressure monitoring should be considered.
Supportive measures are indicated depending on the patient's clinical state.
Benzodiazepines are not significantly removed from the body by dialysis.
Flumazenil, a benzodiazepine antagonist, is not advised as a routine diagnostic test in patients with reduced conscious level. It may sometimes be used as an alternative to ventilation in children who are naive to benzodiazepines, or in patients with COPD to avoid the need for ventilation. It is not necessary or appropriate in cases of poisoning

to fully reverse the benzodiazepine effect. Flumazenil has a short half-life (about an hour) and in this situation an infusion may therefore be required. Flumazenil is contraindicated when patients have ingested multiple medicines, especially after co-ingestion of a benzodiazepine and a tricyclic antidepressant or any other drug that causes seizures. This is because the benzodiazepine may be suppressing seizures induced by the second drug; its antagonism by flumazenil can reveal severe status epilepticus that is very difficult to control.
Contraindications to the use of flumazenil include features suggestive of a tricyclic antidepressant ingestion including a wide QRS, or large pupils. Use in patients postcardiac arrest is also contraindicated.
It should be used with caution in patients with a history of seizures, head injury, or chronic benzodiazepine use.
Occasionally a respirator may be required but generally few problems are encountered, although behavioral changes are likely in children.
If excitation occurs, barbiturates should not be used.
Effects of overdose are more severe when taken with centrally-acting drugs, especially alcohol, and in the absence of supportive measures, may prove fatal.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Benzodiazepine derivatives, ATC code: N05B A01

Diazepam is a benzodiazepine tranquilliser with anticonvulsant, sedative, hypnotic, muscle relaxant and amnesic properties.
Benzodiazepines, such as diazepam, bind to receptors in various regions of the brain and spinal cord. This binding increases the inhibitory effects of gamma-aminobutyric acid (GABA). GABAs functions include CNS involvement in sleep induction. Also involved in the control of hypnosis, memory, anxiety, epilepsy and neuronal excitability.

5.2 Pharmacokinetic properties

Absorption:
Diazepam is readily and completely absorbed from the GI tract. Peak plasma concentrations occurring within about 30-90 minutes of oral administration, a steady plasma concentration is reached after 5-6 days and is directly related to dose.

Distribution:

Diazepam crosses the blood-brain barrier and is highly lipid soluble, this causes the initial effects to decrease rapidly as it is redistributed into fat deposits and tissues. Diazepam is very extensively bound to plasma proteins (98-99%). Diazepam and its metabolites also enters breast milk and crosses the placenta freely, this may lead to accumulation in the infant or foetus.

Metabolism:
Diazepam is extensively metabolised in the liver and, in addition to desmethyldiazepam, its active metabolites include oxazepam and temazepam. Diazepam has a biphasic half-life with an initial rapid distribution phase followed by a prolonged terminal elimination phase of 1 or 2 days; its action is further prolonged by the even longer half-life of 2-5 days of its principle active metabolite, desmethyldiazepam (nordiazepam), the relative proportion of which increases in the body on long-term administration. The plasma half-life of diazepam is prolonged in neonates, in the elderly, and in patients with kidney or liver disease.

Elimination:
It is excreted in the urine, mainly in the form of its metabolites, either free or in conjugated form.

5.3 Pre-clinical Safety Data

Not applicable

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

The product also contains, dextrin, maize starch, lactose, magnesium stearate and indigo carmine lake.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months in polypropylene

24 months in HDPE

36 months in blister foil pack

6.4 Special precautions for storage

Blisters: Do not store above 25°C. Store in the original package to protect from light.
Containers: Do not store above 25°C. Keep the container tightly closed and store in the original container in order to protect from light.

6.5 Nature and Contents of Container

Diazepam tablets are packed in blister packs of 28 tablets or polypropylene or HDPE containers of 21, 100, 250, 500 or 1000 with a low density polyethylene pilfer proof lid.

6.3 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Waymade plc
Trading as Sovereign Medical
Sovereign House
Miles Gray Road
Basildon
Essex SS14 3FR
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 06464/1402

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

3 October 2003

10 DATE OF REVISION OF THE TEXT

20/08/2019