SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Diazepam 5mg/5ml Oral Suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml of suspension contains 5mg of Diazepam BP.

Each 5 ml of suspension also contains 3.75 mg of Ethanol (96 % v/v), 7 mg of Methyl Hydroxybenzoate (E218), 3 mg Propyl Hydroxybenzoate (E216), 50 micrograms Ponceau 4R (E 124) and 1.1g sucrose

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Oral Suspension

Pink raspberry flavoured suspension

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Diazepam has anticonvulsant, anxiolytic, sedative, muscle relaxant and amnesic properties.

It is indicated for:

Adults

i) For the short-term relief (2-4 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;

ii) As a sedative and premedicant;

iii) As an anticonvulsant in the management of status epilepticus, febrile convulsions and poisoning;

iv) In the control of muscle spasms as in tetanus;

v) In the management of alcohol withdrawal symptoms;

vi) In selected cases it may be useful in the management of cerebral spasticity;

Children

i) Night terrors and somnambulism;

ii) Premedication;

iii) In the control of muscle spasms as in tetanus;

iv) In selected cases, it may be useful in controlling tension and irritability in cerebral spasticity;

The use of diazepam to treat short term anxiety is inappropriate and unsuitable. Diazepam should be used to treat insomnia only when it is severe, disabling or subjecting the individual to extreme stress.

4.2 Posology and method of administration

Posology

As an anxiolytic, the lowest effective dose should be employed; dosage regimes should not exceed beyond 14 days.

Patients who have received benzodiazepines for a long time may require an extended withdrawal period. Long-term chronic use is not recommended.

Adults:

Anxiety States: 2mg three times daily up to 30mg daily in divided doses.

Insomnia associated with Anxiety: 5mg to 15mg before retiring.

Muscle Spasms: 2mg to 15mg daily in divided doses up to 60mg in severe spastic disorders such as cerebral spasticity, epilepsy and muscle spasms associated with upper-motor neurone disease.

In the control of muscle spasms as in tetanus: 3mg to 10mg/kg bodyweight daily.

Alcohol Withdrawal Symptoms: 5mg to 20mg repeated within 2 to 4 hours if necessary.

Premedication in Dental Patients: 5mg the night before, 5mg on waking and another 5mg 2 hours before the appointment.

Older people or Debilitated patients: The dosage should be half that recommended in adults.

Use in children and adolescents:

Night Terrors and Somnambulism: 1mg to 5mg daily before retiring.

Premedication: 2mg to 10mg.

Management of Cerebral Spasticity: 2mg to 40mg daily in divided doses.

In the control of Muscle spasms as in Tetanus: 3mg to 10mg/kg bodyweight daily.

Doses should be repeated only on medical advice. Long-term chronic use is not recommended and treatment should always be tapered off gradually.

When a benzodiazepine is used as a hypnotic, treatment should, if possible, be intermittent.

Route of administration

Oral.

Prior to starting treatment with Diazepam, a discussion should be held with patients to put in place a strategy for ending treatment with Diazepam 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. If this medicine is being used for the treatment of epilepsy this medicine should be used for as long as the prescriber considers it necessary.

4.3 Contraindications

Diazepam should not be used in

- Patients with a known hypersensitivity to the active substance, benzodiazepines or to any of the excipients listed in section 6.1;
- Acute pulmonary insufficiency; acute or chronic severe respiratory insufficiency/depression including sleep apnoea syndrome
- myasthenia gravis (condition may be exacerbated);;

severe hepatic impairment (may precipitate encephalopathy)

- phobic or obsessional states, primary treatment of psychotic illness (inadequate evidence of safety and efficacy), hyperkinesis (paradoxical reactions may occur)
- women planning a pregnancy (see section 4.6)
- pregnancy (unless there are compelling reasons – see section 4.6)
- Acute porphyria

Diazepam should not be used as monotherapy in patients with depression or those with anxiety with depression as suicide may be precipitated in such patients.

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, but should not exceed 4 weeks including tapering off process. Treatment should not continue beyond 4 weeks without re-evaluation of the patient's condition.

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 long duration of action such as diazepam, withdrawal phenomena can become manifest between doses, 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.

Diazepam should be used with caution in patients with renal or hepatic dysfunction (see section 4.2 Posology and Method of Administration), porphyria, coma and organic brain changes, particularly arteriosclerosis.

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).

Elderly and debilitated patients

These patients are more prone to the CNS effects of benzodiazepines and, therefore, lower doses are required (see section 4.2 Posology and Method of Administration).

Tolerance

Limits of tolerance in patients with organic cerebral changes (particularly arteriosclerosis) or cardiorespiratory insufficiency may be very wide; care must be taken in adapting the dosage with such patients.

Loss of efficacy to the hypnotic effects may develop after repeated use for a few weeks.

Dependence

The risk of dependence (physical or psychological) increases with dose and duration of treatment and is greater in patients with a history of alcohol or drug abuse, or in patients with a marked personality disorder. Therefore

- regular monitoring of such patients is essential
- routine repeat prescriptions should be avoided
- treatment should be withdrawn gradually

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 diazepam should be reviewed regularly, with frequent assessments of patients being undertaken during the course of their treatment.

Withdrawal effects

The duration of treatment should be as short as possible (see section 4.2).

If physical dependence has developed, abrupt termination of treatment results in withdrawal symptoms. These include headache, muscle pain, extreme anxiety, tension, restlessness, confusion and irritability, sleep disturbance, diarrhoea and mood changes. In severe cases the following may occur: a feeling of unreality or of being separated from the body, depersonalisation, confusional states, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, psychotic manifestations including hallucinations or epileptic seizures. Withdrawal symptoms will be worse in patients with epilepsy, patients who have been dependent on alcohol or other narcotic drugs in the past, but can occur following abrupt cessation of treatment in patients receiving normal therapeutic doses for a short period of time.

Drug withdrawal syndrome

Prior to starting treatment with diazepam, 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 diazepam 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, and for use in epilepsy).

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.

Benzodiazepines: 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.

Rebound symptoms

Symptoms including insomnia and anxiety may occur 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, the dose should be decreased gradually (see section 4.2).

Amnesia

Anterograde amnesia may occur, most often several hours after ingestion. To reduce the risk, patients should ensure that they will be able to have an uninterrupted sleep of 7-8 hours (see also section 4.8). Amnestic effects may be associated with inappropriate behaviour.

Bereavement/loss

Psychological adjustment may be inhibited by benzodiazepines

Psychiatric and 'paradoxical' reactions

Reactions such as restlessness, agitation, irritability, aggressiveness, excitement, confusion, delusions, rage, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects can occur.

These reactions are more likely in children and the elderly, and extreme caution should be used in prescribing benzodiazepines to patients with personality disorders. Should they occur, treatment should be discontinued.

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

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

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

Specific Patient Groups

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.

Patients with depression

Diazepam should not be used alone to treat depression or anxiety associated with depression as suicide may be precipitated in such patients.

Patients with a history of alcohol & drug abuse

Diazepam should be used with extreme caution in patients with a history of alcohol or drug abuse (risk of abuse/dependence).

Patients with phobias and/or chronic psychoses

Diazepam is not recommended (inadequate evidence of efficacy and safety)
Excipients

Diazepam contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine. Also, sucrose may be harmful to the teeth.

Diazepam contains the colouring Ponceau 4R red (E124) which may cause allergic reactions.

Diazepam contains methyl and propyl hydroxybenzoate (E218 and E216). These may cause allergic reactions (possibly delayed).

This medicinal product contains small amounts of ethanol (alcohol), less than 100mg per 5ml.

4.5 Interaction with other medicinal products and other forms of interaction

Not recommended

Alcohol: Diazepam should not be used together with alcohol (enhanced sedative effects: effect the ability to drive or 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.

Anti-epileptic 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. Phenobarbital is a known inducer of CYP3A4 and increases hepatic metabolism of diazepam. Reduced effect of diazepam.. When used concurrently, side effects and

toxicity may be more evident, particularly with hydantoins (eg phenytoin) and/or barbiturates. This requires extra care in adjusting dosage in the initial stages of treatment.

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: cisapride, lofexidine, nabilone, disulfiram and the musclerelaxants baclofen, tizanidine suxethonium and tubocurarin.

Compounds that affect hepatic enzymes (particularly cytochrome P450):

• inhibitors (e.g. 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.

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

Dopaminergics: possible antagonism of the effect of levodopa

Antacids

Concurrent use may delay absorption of diazepam.

Zidivudine

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). Cmax 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 monitered 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.

Fluconazole: 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 ezomeprazole 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 monitered 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.

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).

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 but a causal relationship has not been established.

Women of childbearing potential

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 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 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.

Studies in animals have shown reproductive toxicity (see section 5.3).

Breast-feeding

Since benzodiazepines are found in the breast milk, 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

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you
- It is an offence to drive while under the influence of this medicine
- However, you would not be committing an offence (called 'statutory defence') if:

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

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

o It was not affecting your ability to drive safely.

Patients should be advised that sedation, amnesia, impaired concentration, dizziness, blurred vision and impaired muscular function may occur and that, if affected, they should not drive or to use machines, or take part in other activities where this would put themselves or others at risk. If insufficient sleep duration occurs, the likelihood of impaired alertness may be increased. Concurrent medication may increase these effects (see section 4.5).

4.8 Undesirable effects

Diazepam may cause drowsiness, numbed emotions, reduced alertness, confusion, fatigue, headache, dizziness, muscle weakness, sedation, blurring of vision and ataxia. These may 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]

	Unknown	Drug dependence (see section 4.4)
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) drug withdrawal symptoms (see section 4.4 Special warnings and precautions)[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. 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: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

Benzodiazepines commonly cause drowsiness, ataxia, dysarthria, sedation, muscle weakness, profound sleep, hypotension, bradycardia and nystagmus. In most cases only observation of vital functions is required.

Extreme overdosage may lead to coma, areflexia. Hypotension, respiratory depression and apnoea requiring appropriate counter measures (ventilation, cardiovascular support). . Coma usually lasts only a few hours but in elderly people it may be more protracted and cyclical. Benzodiazepine respiratory depressant effects are more serious in patients with severe chronic respiratory disease. Severe effects in overdose also include rhabdomyolysis and hypothermia.

Benzodiazepines potentiate the effects of other central nervous system depressants, including alcohol.

Management

Maintain a clear airway and adequate ventilation.

Consider activated charcoal in adults or children who have taken more than 1 mg/kg within 1 hour, provided they are not too drowsy.

Gastric lavage is unnecessary if these drugs have been taken alone. Patients who are asymptomatic at four hours are unlikely to develop symptoms.

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.

If CNS depression is severe consider the use of flumazenil (Anexate), a benzodiazepine antagonist. This should rarely be required. It has a short half-life (about an hour) and should NOT TO BE USED IN MIXED OVERDOSE OR AS A "DIAGNOSTIC" TEST. It is contraindicated in the presence of drugs that reduce seizure threshold (e.g. tricyclic antidepressants).

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.

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.

Institute supportive measures as indicated by the patient's clinical state.

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.

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Diazepam has potent anxiolytic anti-convulsant and central muscle relaxant properties, these effects are probably mediated through special areas of the CNS. Diazepam has little autonomic activity.

5.2 Pharmacokinetic properties

Diazepam is readily and completely absorbed from the GI tract, peak plasma concentration occurring within 30-90 minutes of oral administration; the rate of absorption is age related and tends to be delayed in the elderly. Diazepam crosses the blood-brain barrier and is highly lipid soluble. It has a biphasic half-life with an initial rapid distribution phase followed by a prolonged terminal elimination phase of 1-2 days; its action is further prolonged by the even longer half-life of 2-5 days of its active principle metabolite, desmethyldiazepam, the relative proportion of which increases in the body on long-term administration.

Diazepam is extensively metabolised in the liver and, in addition to desmethyldiazepam, its active metabolites include oxazepam and temazepam.

It is excreted in the urine, mainly in the form of its metabolites, either free or in conjugated forms. Diazepam is very extensively bound to plasma proteins.

The half-life of diazepam is prolonged in neonates, in the elderly and in patients with kidney or liver disease. Diazepam and its metabolites cross the placental barrier and are excreted in breast milk.

The following results were obtained following a pharmacokinetic study with healthy volunteers

	Diazepam 5mg/5ml Oral Suspension (Sandoz)
c_{max} (mean ± S.D.)	275 ±73
t_{max} (mean)	1 hour

5.3 Preclinical safety data

None stated

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerin

Sucrose

Microcrystalline cellulose

Methyl hydroxybenzoate(E218)

Propyl hydroxybenzoate(E216)

Ethanol (96 % v/v),
Croscarmellose Sodium
Flavouring Agent (Framboise/Raspberry),
Ponceau 4R (E124)
Potassium sorbate
Purified water

6.2 Incompatibilities

None Known.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store below 25ºC. Protect from light.

6.5 Nature and contents of container

Amber glass bottles with child-resistant caps with plastic inserts.

Pack sizes: 50 ml, 100 ml, 150 ml, 250 ml, 300 ml and 500 ml.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Shake well before use.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

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