SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Diazepam Tablets 5mg BP

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5mg Diazepam B.P

3 PHARMACEUTICAL FORM

Uncoated compressed tablets
White, flat, circular tablets with a bevelled edge and breaklined. Embossed ‘D/5’ on one face, ‘PV’on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Diazepam is indicated for short term use (up to 4 weeks) and only when the disorder is severe, disabling or subjecting the patients to extreme distress.

The use of benzodiazepines to treat short-term "mild" anxiety is considered to be inappropriate and unsuitable.

Adults:

- symptomatic treatment of anxiety occurring alone or in association with insomnia or short term psychosomatic, organic or psychotic illness.
- Treatment of conditions where anxiety may be precipitating or aggravating factor such as migraine attacks or tension headaches.
- Muscle spasm
- Adjunct to the control of muscle spasm in tetanus.
- Management of selected cases of cerebral spasticity.
- Symptomatic treatment of acute alcohol withdrawal.
- Adjunct to the management of some types of epilepsy such as myoclonus.

- As premedication

Children:

- Adjunct to control of muscle spasm in tetanus.
- Controlling tension and irritability in selected cases of cerebral spasticity.
- As pre-medication (but only with extreme caution –see section 4.4)

4.2 **Posology and method of administration:**

Route of administration: oral. Tablets should be swallowed with water

Treatment to be given under close medical supervision at the lowest effective dose for the shortest possible duration (not exceeding 4 weeks)
Extension of use should not take place without further clinical evaluation

Chronic use not recommended (little is known of the long term safety and efficacy: potential for dependence- see section 4.4).

When treatment is started the patient should be informed that treatment will be of limited duration the dosage will be progressively decreased there is the possibility of rebound phenomena (thereby minimising concerns about symptoms that may develop on dose reduction)

Anxiety
Adults
Patients should not be started on 5mg and 10mg tablets as the usual starting dose is 2mg three times daily (use lowest effective dose).
Usual dose 2-5 mg three times daily (adjusted to individual response)
Maximum -30mg daily (in divided doses)

Insomnia associated with anxiety-5 to 15mg before retiring
Treatment should not continue at full dose for more than 2 weeks with a 2 week tapering off process.

Symptomatic relief of acute alcohol withdrawal
Adults
5-20mg, repeated if necessary in 2 to 4 hours

Conditions associated with muscle spasm

- Adults-muscle spasm

Usual dose 2-15mg in divided dose (maximum -15mg daily)

- Adults-cerebral palsy/spasticity (selected cases)

Usual dose 2-60mg daily in divided doses(maximum 60mg)

- Children/adolescents-cerebral palsy (selected cases)

Child 5-12 years- initially 5mg twice a day
Adolescent 12 to 18 years-initially 10mg twice daily

Maximum -40mg daily in divided doses

- Adults and children/adolescents –control of muscle spasm in tetanus

3-10mg/kg daily by nasogastric tube
Selected dose should relate to the severity of the symptoms
In extremely severe cases higher doses have been used

Premedication
Adults
5-20mg before the procedure
Children
Use with extreme caution (increased risk of inappropriate response- see section 4.4)
2-10mg before the procedure

Adjunct to management of some types of epilepsy
Adults
Usual dose 2-60mg in divided doses (maximum 60mg daily)

Circumstances/conditions where dose reduction may be needed
Elderly and/or debilitated patients (see below)
Patients with impaired hepatic and/or renal function (see below)
Patients with organic cerebral changed and/or cardiorespiratory disorder (see below & section 4.4)
Hypoalbuminaemia (see section 4.4)
Patient taking azole antifungals and other drugs affecting hepatic enzymes (see section 4.5)

Special populations
Elderly and/or debilitated patients
Dosage should not exceed half the adult dose (increased sensitivity to CNS effects)

Patients with impaired hepatic or renal function
Hepatic impairment-dose should not exceed half the adult dose and steps should be taken to ensure that there is no accumulation of plasma diazepam: consider alternative drug
Contraindicated in severe hepatic insufficiency (see section 4.3)
Severe renal impairment-dose should be reduced (cerebral sensitivity increased)

Patient with organic cerebral changes and/or cardiorespiratory disorders (see section 4.4)
Limits of tolerance very wide
Care with dose selection/revision

Patients who have taken benzodiazepines for prolonged time may require a longer period of dosage reduction and specialist help may be appropriate.

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

- Hypersensitivity to benzodiazepines and any other ingredients of diazepam tablets
- Acute pulmonary insufficiency, respiratory depression: sleeps apnoea syndrome (risk of further respiratory depression.
- Phobic or obsessional states/ chronic psychosis (inadequate evidence of safety and efficacy).
- Severe hepatic insufficiency (may precipitate encephalopathy)
- Planning a pregnancy (see section 4.6)
- Pregnancy (unless there are compelling reasons –see section 4.6)
- Myasthenia gravis (increased muscle weakness)
- Acute porphyria (may precipitate an attack)

Diazepam should not be used alone in depression or anxiety with depression (may precipitate suicide). They should not be used for the treatment of chronic psychosis, hyperkinesis (paradoxical reactions may occur). Amnesia may occur.

Suicide may be precipitated in patients who are depressed and aggressive behaviour towards self and others may be precipitated. Extreme caution should therefore be used in prescribing benzodiazepines in patients with personality disorders.

Withdrawal from benzodiazepines may be associated with physiological and psychological symptoms of withdrawal including depression. Withdrawal symptoms may occur following normal therapeutic doses given for short periods of time.

An underlying cause of insomnia should be sought before deciding upon the use of benzodiazepines for symptomatic relief.

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

4.4 Special warnings and precautions for use:

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. Where long-term therapy is essential, it is recommended that the patient's requirements be reviewed on a regular basis.

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.

Tolerance

Limits of tolerance in patients with organic cerebral changes (particularly arteriosclerosis) or cardio-respiratory insufficiency may be very wide. Care with dose selection/revision required (see section 4.2)

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).

Dependence

Use of diazepam may lead to the development of physical and psychic dependence.

The dependence potential on benzodiazepines is low, particularly when restricted to short term use, when high doses are used this increases, especially when given over long periods. The risk of dependence is greater in patients with 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 and treatment should be withdrawn gradually. Moreover it is important that the patient should be aware of the possibility of rebound phenomena, thereby minimizing anxiety over such symptoms should occur while diazepam Is being discontinued.

Withdrawal effects

The duration of treatment should be as short as possible (see section 4.2). Withdrawal symptoms occur with benzodiazepines following normal therapeutic doses given for short periods of time.

If physical dependence has developed, abrupt termination results in withdrawal symptoms (see section 4.8). 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, confusion state, numbness and tingling of extremities, hypersensitivity of light, noise and physical contact, psychotic manifestations including hallucinations, or epileptic seizures (particular care in patients with history of fits/seizures).

Withdrawal symptoms will be worse in patients who have been dependent on alcohol or other narcotic drugs in the past (particular care required), but can occur following abrupt cessation in patients on normal therapeutic doses for short period of time.

When diazepam is being used it is important not to change to a benzodiazepine with short duration of action ,as withdrawal symptoms may be precipitated.

Rebound symptoms

Rebound insomnia and anxiety may occur. This is a transient syndrome where the
symptoms that led to the use of diazepam recur in an enhanced form
Symptoms including insomnia, anxiety, mood changes and restlessness may occur on withdrawal of treatment. As this is greater after abrupt discontinuation, the dose should be decreased gradually (see section4.2)

Amnesia

Benzodiazepines may induce anterograde amnesia. Amnestic effects may be associated with inappropriate behaviour. Anterograde amnesia may occur using therapeutic doses, the risk increases with higher doses. This condition 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).

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.

Hypoalbuminaemia

Possible increased incidence of sedatives side effects (consider reduced dose)

Specific Patient Groups

- *Elderly (see section 4.2)*
  Avoid in those at risk of becoming confused and/or ataxic (increased likelihood of a fall and injury to themselves) if, based on clinical need, a decision to treat is nevertheless taken, start treatment at a lower dose.

- *Children-use as pre-medication*
  Extreme caution required as the effects and timing of action/response of diazepam used peri-operatively in children may be unreliable and/or paradoxical effects may occur.

- *Patients with depression*

  Diazepam should not be used alone to treat depression or anxiety associated with depression as may precipitate suicide.

- *Patients with a history of alcohol &drug abuse*

  Use with extreme caution (risk of abuse/dependence).

- *Patients with phobias and/or chronic psychoses*

  Not recommended (inadequate evidence of efficacy and safety- see section 4.3)

  *Patients with marked personality disorder*Use with extreme caution

- *Patients with severe hepatic insufficiency*

  Not recommended (may precipate encephalopathy)

- *Patients with chronic pulmonary insufficiency, and patients with chronic hepatic disease*

  May require a reduced dosage.

In renal failure the half-life of diazepam is unchanged and therefore no dosage adjustments are required in these patients.

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

Intolerance to sugars (see section 4.3)

WARNING: These tablets should not be given to patients with rare hereditary problems of galactose intolerance, the Lapp lactose deficiency or glucose-galactose malaabsorption.

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.

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.

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.

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: impaired ability to drive/operate machinery).

Sodium oxybate
Avoid concomitant use(enhance effects of sodium oxybate)

HIV-protease inhibitors
Avoid concomitant use (increased risk of prolonged sedation)-see below for zidovudine.

Take into account

Centrally acting drugs

Enhancing of the central depressive effect may occur if diazepam is combined with drugs such as neuroleptics, antipsychotics, anxiolytics/sedatives, tranquilisers, antidepressants, hypnotics, anticonvulsants, analgesics, anaesthetics, barbiturates and sedative antihistamines. The elderly may require special supervision.

Anti-epileptics drugs

Pharmacokinetics studies on potential interactions between diazepam and antiepileptic drugs have produced conflicting results. Depression and elevation of drugs levels, as well as no change, have been reported.

Phenobarbital taken concomitantly may result in an additive CNS effect. 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).

There have also been reports that the metabolic elimination of phenytoin is affected
by diazepam.

Narcotic analgesics
Enhancement of the euphoria may lead to increased psychological dependence. The elderly require supervision.

Other drugs enhancing the sedatives effect of diazepam
Cisapride, lofexidine, nabilone, disulfiram and the muscle-relaxants –baclofen and tizanidine. Cisparide may lead to a temporary increase in the sedative effects of orally administered benzodiazepines due to faster absorption.

Compounds that affect hepatic enzymes (particularly cytochrome p450):
Inhibitors of hepatic enzymes (e.g cimetidine, isoniazid, erythromycin, omeprazole, esomeprazole, fluvoxamine and fluoxetine) reduce clearance and may potentiate the action of benzodiazepines. Itraconazole, ketoconazole, and to lesser extent fluconazole and voriconazole are potent inhibitors of the cytochrome P450 isoenzymes CYP3A4 and may increase plasma levels of benzodiazepines. The effect of benzodiazepines may be increased and prolonged by concominant use. A dose reduction of the benzodiazepine may be required.

Inducers of hepatic enzymes (e.g. rifampicin) may increase clearance of benzodiazepines.

Antihypertensives,vasodilators & diuretics:
Enhanced hypotensives effect with ACE-inhibitors, alpha-blockers, angiotensin-II receptor antagonists, calcium channel blockers adrenergics neurone blockers, beta-blockers, moxonidine, nitrates, hydralazine, minoxidil, sodium nitroprusside and diuretics.
Enhanced sedatives effects with alpha- blockers or moxonidine

Dopaminergics
Possible antagonism of the effect of levodopa

Antacids
Concurrent use may delay absorption of diazepam

Zidivudine
Increased zidovudine clearance by diazepam

Oestrogen-containing contraceptives
Possible inhibition of hepatic metabolism of diazepam.

Theophylline
Increased metabolism of diazepam which possibly reduces the effect.

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

Grapefruit juice
Inhibitation of CYP3A4 may increase the plasma concentration of diazepam (possible increased sedation and amnesia). This interaction may of little significance in healthy individuals , but it is not clear, if other factors such as old age or liver cirrhosis increase the risk of adverse effects with concurrent use.

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.

Do not use during pregnancy, if the product is prescribed to a women of child bearing potential, she should be warned to contact her physician regarding discontinuance of the product, if she intend to become or suspect that she is pregnant.

If, for compelling reasons, the product is administered during the late phase of pregnancy, or during labour at high doses irregularities in foetal heart rate have been reported, effect on the neonate such as hypothermia, hypotonia, poor sucking and moderate respiratory depression can be expected, due to the pharmacological action of the compound.

With newborn infants it must be remembered that the enzyme system involved in the breakdown of the drug is not yet fully developed (especially in premature infants). Moreover, infants born to mother who took benzodiazepines chronically during the later stage of pregnancy may have developed physical dependence and may be at some risk for developing withdrawal symptoms in the postnatal period.

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

4.7 Effects on ability to drive and use machines

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 other at risk.

- These are dose related and may persist into the following day, even after a single dose. If insufficient sleep duration occurs, the likelihood of impaired alertness may be increased.
- Impaired function and sedation may last for several days.
- Concurrent medication may increase these effects (see section 4.5).

Patients should be warned of the possible hazard when driving or operating machinery. These effects may be potentiated by alcohol. The elderly and the debilitated are particularly liable to experience these symptoms together with confusion, especially if organic brain symptoms are present.

4.8 **Undesirable effects:**

Dose related adverse effects which occur commonly with diazepam and which may persist into the following day, even after a single dose includes sedation, drowsiness, unsteadiness and ataxia.
During the first week of administration or when high doses are used they may have a
sedative effect and cause some degree of drowsiness. In such cases there is an advantage in administering half the total daily intake at night, the remainder being
given in divided doses during the day. The elderly and debilitated are particularly sensitive to the effect of centrally-depressant drugs and may experience confusion, especially if organic brain changes are present, the dosage of diazepam should not exceed one-half that recommended for other adults.

The most commonly reported undesirable effects are drowsiness, reduced alertness
and muscle weakness. These phenomena occur predominantly at the start of therapy
and usually disappear with prolonged administration.
Pre-existing depression may be unmasked during benzodiazepine use.
Chronic use (even at therapeutic doses) may lead to the development of physical and psychological dependence (see 4.4 Special warnings and special precautions for use).

Skin and subcutaneous tissue disorder
Allergic reactions (skin rash or itching) occur rarely.

Central and peripheral nervous disorders

Drowsiness, sedation, unsteadiness, ataxia is common (these effects are dose-related and may persist into the following day even after a single dose).
Headache, light headedness, vertigo, dystonic effects occur rarely. Impaired

motor ability, dizziness, muscle weakness, tremor, dysarthia and slurred speech.

Vision disorders

Blurred vision. Diplopia
Visual disturbances occur rarely.

Psychiatric disorders

Libido fluctuations occur rarely. Depression, Anterograde amnesia (amnesia may be associated with inappropriate behaviour, see 4.4 Special warnings and precautions for use), concentration difficulties, abnormal psychological reactions, behavioural adverse effects include paradoxical aggressive outbursts, excitement, confusion, restlessness, agitation, irritability, aggressiveness, delusions, rages, nightmares, hallucinations, psychoses, inappropriate behaviour, numbed emotions and the uncovering of depression with suicidal tendencies and dependence. Diazepam should not be used alone to treat depression or anxiety associated with depression, since suicide may be precipitated in such patients (see section 4.4). Abuse of benzodiazepines has been reported. Drug dependence (see section 4.4)

Gastro-intestinal system disorders

Gastrointestinal upsets occur rarely. Increased salivary secretion, gastrointestinal disturbances, constipation, nausea, dry mouth.

Hepatobiliary disorders

Jaundice occurs rarely.
Very rarely elevated transaminases and alkaline phosphatases.

Endocrine disorders
Gynaecomastia.

Cardio disorders

Hypotension occurs rarely.

Respiratory system disorders

Respiratory depression, apnoea.

Blood disorders

Blood dyscrasias occur rarely.

Urinary system disorders

Urinary retention occurs rarely.

Incontinence

General disorders and administration site conditions

Fatigue most commonly reported. Anaphylaxis.

Drug withdrawal symptoms (see 4.4 Special warnings and precautions)

The elderly and patients with impaired hepatic function will be particularly susceptible to the adverse effects listed above. It is advisable to review treatment
regularly and to discontinue use as soon as possible.
Discontinuation of therapy may result in withdrawal or rebound phenomena.

Withdrawal effects

Withdrawal symptoms: Development of dependence is common after regular use, even in therapeutic doses for short periods, particularly in patients with a history of drug or alcohol abuse or marked personality disorders. Discontinuation of the therapy may result in withdrawal or rebound phenomena (see 4.4 Special Warnings and Special Precautions for Use). Symptoms of benzodiazepine withdrawal include anxiety, depression, impaired concentration, insomnia, headache, dizziness, tinnitus, loss of appetite, tremor, perspiration, irritability, perceptual disturbances such as hypersensitivity to physical, visual, and auditory stimuli and abnormal taste, nausea, vomiting, abdominal cramps, palpitations, mild systolic hypertension, tachycardia, and orthostatic hypotension.

Rare and more serious symptoms include muscle twitching, confusional or paranoid psychosis, convulsions, hallucinations, and a state resembling delirium tremens. Broken sleep with vivid dreams and increased REM sleep may persist for some weeks after withdrawal of benzodiazepines.

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:
United Kingdom
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.'

4.9 **Overdose**

Benzodiazepines potentiate the effects of other CNS depressants including alcohol.

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.

Features
The common symptoms of diazepam overdose are mainly an intensification of the therapeutic effects (ataxia, drowsiness, dysarthria, sedation, muscle weakness and nystagmus) or paradoxical excitation. Coma hypotension, bradycardia and respiratory depression can occur. Coma usually lasts only a few hours but may be prolonged in elderly patients. 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

- Supportive measures are indicated depending on the patient's clinical state. Patients who are asymptomatic at 4 hours are unlikely to develop severe toxicity. If excitation occurs, barbiturates should not be used.

- Maintain a clear airway and adequate ventilation.

- Consider activated charcoal (50g for an adult, 1g/kg for child) in adults who have taken more than 100mg or children who have taken more than 1mg/kg within one hour, provided the airway can be protected.

- 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.

- Benzodiazepines are not significantly removed from the body by dialysis.

- Flumazenil should only be used by an anaesthetist or a doctor with experience in anaesthesiology. It should not be used as a routine diagnostic test or in mixed overdoses. It has a short half-life(about an hour) and the benzodiazepine may be suppressing seizures induced by the second drug and antagonism of this effect can result in severe status epilepticus that is very difficult to control.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: N05B A01

Diazepam is long acting benzodiazepines with anxiolytic, anticonvulsant, skeletal muscle relaxant, and sedative hypnoticactivity. The benzodiazepines are believed to act as agonist at the benzodiazepines receptors (BZ1 and BZ2) in the brain. Through the BZ-GABA receptor chloride ionopore complex, they facilitate or amplify the inhibitory activity of GABA.

5.2 Pharmacokinetic properties

Diazepam is well absorbed after oral administration with peak blood level being achieved within one to two hours and with a rapid onset of clinical effects. It is very highly (98%) protein bound in the plasma and has a long half life of 20 – 70 hours. Diazepam is metabolised by oxidation to active and inactive metabolites which are then conjugated with glucuronic acid and eliminated by the kidneys. The active metabolites-desmethyldiazepam temazepam and oxazepam- have half-lives of 30 - 100, 9.5 - 12.4 and 5 - 15 hours respectively. The half lives of parent drug and active metabolites may be prolonged in the elderly, children and patient with hepatic disease. With repeated dosing, parent drug and metabolites accumulate. The metabolites may take up to two week to reach steady state and can attain higher concentration than the parent compound.

5.3. Pre-clinical Safety Data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lactose
Maize starch
Tartrazine Lake
Magnesium Stearate
Colloidal silicon dioxide
Explotab

6.2. Incompatibilities

None known.

6.3. Shelf life

5 years.

6.4. Special precautions for storage

Will be stored in a cool, dry place protected from right light.

6.5 Nature and contents of container

Nature and content of the container:

Plastic securitainers with tamper evident polypropylene lids (Materials comply to EEC directives for plastics in contact with drugs and foodstuffs).
Packed in pack sizes: 28, 30, 50, 56, 100, 250, 500 and 1000

Aluminium / opaque PVC blister packs as an additional immediate packaging for all pack sizes currently registered.

Not all pack sizes may be marketed.

6.6. Instruction for use and handling

None.

7. MARKETING AUTHORISATION HOLDER

Pharmvit Limited
Unit 13, Metropolitan Centre
Derby Road
Greenford
Middlesex UB6 8UJ

8. MARKETING AUTHORISATION NUMBER

PL 04556/0017

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

1/05/1985

10 DATE OF REVISION OF THE TEXT

16/01/2026