

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Arrow – Diazepam 2, tablets, 2 mg

Arrow – Diazepam 5, tablets, 5 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2 mg or 5 mg of diazepam.

Excipient with known effect: lactose

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Arrow - Diazepam 2: White, round, flat-bevel edged tablet embossed with 'D2' on one side and breakline on the other side. Each tablet contains diazepam 2 mg.

Arrow - Diazepam 5: Yellow, round, flat-bevel edged tablet embossed with 'D5' on one side and breakline on the other side. Each tablet contains diazepam 5 mg.

The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults

Short-term (2 to 4 weeks) symptomatic treatment 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.

Short-term (2 to 4 weeks) treatment of conditions where anxiety may be a precipitating or aggravating factor, e.g. tension headaches or migraine attacks.

Symptomatic treatment of acute alcohol withdrawal.

Muscle spasm. As an adjunct to the control of muscle spasm in tetanus.

May be useful in the management of cerebral spasticity in selected cases.

As an adjunct to the management of some types of epilepsy, e.g. myoclonus.

Premedication.

Children

Night terrors and somnambulism.

May be useful in controlling tension and irritability in cerebral spasticity in selected cases.

As an adjunct to the control of muscle spasm in tetanus.

Premedication.

4.2 Dose and method of administration

This product may not be interchangeable with other products containing this ingredient in the New Zealand's market.

Anxiety states

Adults: Usual dose: 2 mg three times daily.

Maximum dose: Up to 30 mg daily in divided doses. Adjusted on an individual basis.

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

The lowest dose which can control symptoms should be used. Treatment should not be continued at the full dose beyond four weeks. Long-term chronic use is not recommended. Treatment should always be tapered off gradually. Patients who have taken benzodiazepines for a prolonged time may require a longer period during which doses are reduced. Specialist help may be appropriate.

Symptomatic relief of acute alcohol withdrawal

Adults: 5 to 20 mg, repeated if necessary in 2 to 4 hours.

Night terrors and somnambulism

Children: 1 to 5 mg at bedtime.

Conditions associated with muscle spasm:

Adults:

Muscle spasm: 2 to 15 mg daily in divided doses.

Management of cerebral spasticity in selected cases: 2 to 60 mg daily in divided doses.

Adjunct to control of muscle spasm in tetanus: 3 to 10 mg/kg bodyweight daily by nasoduodenal tube.

The selected dose should relate to the severity of the case and in extremely severe cases higher doses have been used.

Children:

Control of tension and irritability in cerebral spasticity in selected cases: 2 to 40 mg daily in divided doses.

As an adjunct to the control of muscle spasm in tetanus: As for adults.

Adjunct to the management to some types of epilepsy:

Adults: 2 to 60 mg daily in divided doses

Premedication:

Adults: 5 to 20 mg

Children: 2 to 10 mg

Special populations

Elderly or debilitated patients: Doses should not exceed half those normally recommended.

4.3 Contraindications

Diazepam should not be given to patients with acute closed-angle glaucoma, or a predisposition to it, myasthenia gravis, severe chronic obstructive pulmonary disease, hyperkinesia and children with swallowing abnormalities.

Diazepam should also be avoided in psychotic patients with mental illness or suicidal tendencies unless there is a marked component of anxiety.

Also avoid use in patients with hypersensitivity to diazepam.

Diazepam is also contraindicated in acute alcohol intoxication with depressed vital signs.

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 (see Section 4.4. Special warnings and precautions for use).

4.4 Special warnings and precautions for use

An underlying cause for insomnia should be sought before deciding upon the use of benzodiazepines for symptomatic relief. In patients with chronic pulmonary insufficiency, and in patients with chronic renal or hepatic disease, dosage may need to be reduced.

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

Abnormal psychological reactions to benzodiazepines have been reported. Rare behavioural effects include paradoxical aggressive outbursts, excitement, confusion, and the uncovering of depression with suicidal tendencies.

Disinhibiting effects may be manifested in various ways. 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 to patients with personality disorders.

In patients with myasthenia gravis, who are prescribed diazepam, care should be taken on account of pre-existing muscle weakness.

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

Treatment should be kept to a minimum and given only under close medical supervision. Little is known regarding the efficacy or safety of benzodiazepines in long-term use.

Duration of Treatment

For patients with anxiety and/or insomnia the duration of treatment should not exceed 4 weeks (including the tapering off process).

Continuous long term treatment is not recommended, but intermittent use may be appropriate.

Where long-term therapy is considered essential, the patient should be regularly reviewed.

Tolerance

Tolerance to benzodiazepines may develop from continued therapy. There is evidence that tolerance develops to the sedative effects of benzodiazepines.

Dependence and Withdrawal

Use of benzodiazepines may lead to the development of physical and psychological dependence. The risk of dependence increases with dose and duration of treatment. Development of dependence is common after regular use of diazepam, particularly in patients with a history of drug or alcohol abuse or marked personality disorders. Regular monitoring in such patients is essential, routine repeat prescriptions should be avoided and treatment should be withdrawn gradually. Dependence can occur even with therapeutic doses administered for short periods of time.

Abrupt discontinuation or rapid dosage reduction of diazepam therapy may result in withdrawal or rebound phenomena. The likelihood and degree of severity of withdrawal symptoms is dependent on the duration of treatment, dose level and degree of dependency.

Withdrawal from benzodiazepines may be associated with physiological and psychological symptoms of withdrawal including depression. 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 hypertension.

Withdrawal symptoms occur with benzodiazepines following normal therapeutic doses given for short periods of time. Symptoms such as depression, nervousness, rebound insomnia, irritability, sweating and diarrhoea have been reported following abrupt cessation of treatment in patients receiving even normal therapeutic doses for short periods of time.

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. More serious manifestations of withdrawal are more common in patients who have received excessive doses over a prolonged period, or in patients who have been dependent on alcohol or other narcotic drugs in the past.

The diazepam dose should be tapered gradually to minimise the occurrence of withdrawal symptoms. Patients should be advised to consult their physician before either increasing the dose or abruptly discontinuing the medication. An individualised withdrawal timetable needs to be planned for each patient in whom dependence is known or suspected.

A sudden discontinuation of benzodiazepines may result in convulsion. Particular care should be taken in patients with epilepsy, and other patients who have had a history of seizures, alcohol or drug dependence.

In some cases, patients taking benzodiazepines have developed protracted withdrawal syndrome with withdrawal symptoms lasting weeks to more than 12 months.

Amnesia

Benzodiazepines may induce anterograde amnesia. Anterograde amnesia may occur even if benzodiazepines are used within the normal dose range, though this is seen in particular at high dose levels. The condition occurs most often several hours after ingesting the product. Therefore to reduce the risk, patients should ensure that they will be able to have an uninterrupted sleep of 7-8 hours. Amnesic effects may be associated with inappropriate behaviour.

Psychiatric and/or paradoxical reactions

Paradoxical reactions such as restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects have been reported during the use of benzodiazepines. These reactions are more likely to occur in children and elderly patients. Should these reactions occur, treatment with diazepam should be discontinued.

As with other benzodiazepines and CNS active drugs, three idiosyncratic symptom clusters which may overlap have been described.

- *Amnesic symptoms*: anterograde amnesia with appropriate or inappropriate behaviour
- *Confusional states*: disorientation, derealisation, depersonalisation and/or clouding of consciousness
- *Agitational states*: sleep disturbances restlessness, irritability, aggression and excitation.

Depression

Depression has been reported with therapeutic use and withdrawal of benzodiazepine therapy. The disinhibiting effects of benzodiazepines may also play a role in the precipitation of suicide attempts or completed suicides. Therefore, benzodiazepines should be used with caution and the prescription size should be limited in patients with signs and symptoms of a depressive disorder or suicidal tendencies.

Use in the elderly

Benzodiazepines should be used with caution in elderly patients due to a greater susceptibility to adverse effects such as dizziness, ataxia and confusion which may increase the risk of falls and

consequent injury. Lower doses should be used in elderly patients (see Section 4.2 Dose and method of administration).

Paediatric population

Benzodiazepines should not be given to children without careful assessment. 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.

Abuse

Abuse of benzodiazepines has been reported. Before prescribing and throughout treatment, assess each patient's risk for abuse, misuse and addiction. Because of a risk of abuse, repeat prescriptions should not be given without medical review.

Benzodiazepines should be used in caution in patients with a history of alcohol or drug abuse, dependence on CNS depressants, those known to be addiction prone or those whose history suggests they may increase the dosage on their own initiative. Use of benzodiazepines, particularly patients at elevated risk, necessitates counselling about the risks and proper use.

Concomitant use with alcohol/CNS depressants

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 which may include severe sedation, clinically relevant respiratory and/or cardiovascular depression (see Section 4.5 Interactions with medicines and other forms of interaction).

Risks from Concomitant Use with Opioids

Concomitant use of benzodiazepines, including diazepam, and opioids may result in profound sedation, respiratory depression, coma, and death. Because of these risks, reserve concomitant prescribing of benzodiazepines and opioids for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. If a decision is made to prescribe diazepam concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use, and follow patients closely for signs and symptoms of respiratory depression and sedation. Advise both patients and caregivers about the risks of respiratory depression and sedation when diazepam is used with opioids (see Section 4.5 Interactions with other medicines and other forms of interaction).

4.5 Interaction with other medicines and other forms of interaction

Alcohol

Concomitant intake with alcohol is not recommended. The sedative effect may be enhanced when the product is used in combination with alcohol. This affects the ability to drive or use machines.

Other CNS depressant medicinal products

If diazepam is given concomitantly with centrally-acting drugs such as neuroleptics, tranquillisers, antidepressants, hypnotics, analgesics and anaesthetics, the sedative effects are likely to be intensified. The elderly require special supervision.

The concomitant use of benzodiazepines and opioids increases the risk of respiratory depression because of actions at different receptor sites in the CNS that control respiration. Benzodiazepines interact at GABA_A sites, and opioids interact primarily at mu receptors. When benzodiazepines and opioids are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists. Limit dosage and duration of concomitant use of benzodiazepines and opioids, and follow patients closely for respiratory depression and sedation.

Pharmacokinetic studies on potential interactions between diazepam and anti-epileptic drugs have produced conflicting results. Both depression and elevation of drug levels, as well as no change, have been reported.

When diazepam is used in conjunction with anti-epileptic drugs, side-effects and toxicity may be more evident, particularly with hydantoins or barbiturates or combinations including them. This requires extra care in adjusting dosage in the initial stages of treatment.

Phenobarbital

Phenobarbital increases the risk of sedation and respiratory depression when co-administered with diazepam due to the additive CNS-depressant effects.

Also, phenobarbital is a known CYP3A4 inducer and increases the hepatic metabolism of diazepam, thus decreasing its effects.

Clozapine

When taken concomitantly with diazepam, treatment with clozapine may lead to severe hypotension, respiratory depression, unconsciousness and potentially fatal respiratory and/or cardiac arrest due to synergistic CNS depressant effects. Therefore, concomitant use of diazepam and clozapine is not recommended and should be avoided.

Opioids

The concomitant use of sedative medicines such as benzodiazepines or related drugs 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 Special warnings and precautions for use).

Theophylline

When this medicinal product is concomitantly administered with theophylline, inhibition of the pharmacodynamic effects of diazepam may occur, e.g. reduction of sedation and psychomotor effects.

This possibly occurs due to competitive binding of theophylline to adenosine receptors in the brain.

Muscle relaxants (suxamethonium, tubocurarin)

Modified intensity of neuromuscular blockage may occur.

Hepatic metabolism

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 can result in substantially decreased plasma concentrations of diazepam.

CYP3A4 and CYP2C19 inducers

Medicinal products that are known inducers of CYP3A4 can substantially increase the hepatic metabolism and clearance of diazepam. Concomitant administration of CYP inducers and diazepam can lead to significantly decreased effects of diazepam. Therefore, concomitant use of diazepam is not recommended with rifampicin, carbamazepine, phenytoin, phenobarbital, etc.

When diazepam is co-administered with corticosteroids, it may lead to increased metabolism of diazepam due to induction of CYP3A4 enzyme, or enzymes responsible for glucuronidation of diazepam.

CYP3A4 and CYP2C19 inhibitors

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 may occur when these medicinal products are concomitantly used with diazepam. Therefore, concomitant use should be avoided.

Azoles (fluconazole, itraconazole, ketoconazole, voriconazole)

Co-administration of azole antifungals may lead to increased plasma concentration of benzodiazepines, due to inhibition of the CYP3A4 and/or CYP2C19 metabolic pathway.

When these medicinal products are concomitantly used, increased risk of undesired effects and toxicity of diazepam may occur. 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 of diazepam. When fluvoxamine is co-administered with diazepam, drowsiness, reduced psychomotor performance and memory may occur. Preferably, benzodiazepines that are metabolised via a non-oxidative pathway should be used instead.

Cimetidine

Cimetidine inhibits the hepatic metabolism of diazepam, reducing its clearance and prolonging its half-life. This interaction leads to increased effects of diazepam and increased risk of drowsiness. Reduction of the diazepam dose may be necessary.

Omeprazole, esomeprazole

Omeprazole and esomeprazole inhibit the CYP2C19 metabolic pathway for diazepam, resulting in an increased half-life and concentrations of diazepam. This leads to increased effects of diazepam. Reduction of the diazepam dose may be necessary.

Isoniazid

Isoniazid inhibits the CYP2C19 and CYP3A4 metabolic pathway for diazepam. This leads to increased effects of diazepam.

Fluoxetine

Fluoxetine inhibits the metabolism of diazepam via CYP2C19 and other pathways, resulting in elevated plasma concentrations and decreased clearance of diazepam. This can lead to 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.

Oral contraceptives

Effect on diazepam: Inhibition of oxidative metabolism of diazepam.

Effect on oral contraceptives: Co-administration of diazepam and combined oral contraceptives has been known to cause breakthrough bleeding. The mechanism of this reaction is unknown.

Grapefruit juice

Grapefruit juice is believed to inhibit CYP3A4 and increases the plasma concentration of diazepam. This may lead to increased effects of diazepam.

Other

Cisapride

When administered concomitantly with diazepam, cisapride may cause accelerated absorption of diazepam. This may result in temporary increase of the sedative effects of orally administered diazepam.

Levodopa

Concomitant use with diazepam may result in reduced effects of levodopa.

Valproic acid

Valproate displaces diazepam from its plasma albumin binding sites and inhibits its metabolism. This can lead to increased serum concentrations of diazepam.

Ketamine

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

4.6 Fertility, pregnancy and lactation

Use in pregnancy

Category C

If the product is prescribed to a woman of childbearing potential, she should be warned to contact her physician regarding discontinuance of the product if she intends to become or suspects that she is pregnant.

There are limited amount of data from the use of diazepam in pregnant women. Studies in animals have shown reproductive toxicity.

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 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.

Use in lactation

Since benzodiazepines are found in 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

Diazepam has a significant influence on the ability to drive and to operate machines.

During treatment with diazepam, undesirable effects such as impaired motor skills, tremor, somnolence, amnesia, impaired concentration and tiredness may occur.

The effect can be observed immediately after the start of treatment and can last for several days following discontinuation due to the long half-life of diazepam.

If insufficient sleep duration occurs, the likelihood of impaired alertness may be increased (see Section 4.5 Interactions with other medicines and other forms of interaction).

Patients should be advised that, like all medicaments of this type, diazepam may modify patients' performance at skilled tasks (driving, operating machinery, etc) to a varying degree depending on dosage, administration and individual susceptibility. Patients should further be advised that alcohol may intensify any impairment and should, therefore be avoided during treatment.

4.8 Undesirable effects

Summary of the safety profile

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, particularly in children.

Amnesia

Anterograde amnesia may occur using therapeutic dosages, the risk increasing at higher dosages. Amnesic effects may be associated with inappropriate behaviour.

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. Abuse of benzodiazepines has been reported.

List of adverse reactions

The frequencies of adverse events are ranked according to the following: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

Blood and lymphatic system disorders

Very rare: Leukopenia

Immune system disorders

Not known: Anaphylactic reaction

Metabolism and nutrition disorders

Rare: Increased appetite

Psychiatric disorders

Rare: Increased or decreased libido

Not known: Confusional state, psychiatric and paradoxical reactions, numbed emotions, depression

Nervous system disorders

Common: Ataxia

Uncommon: Balance disorders

Rare: Loss of consciousness, insomnia

Not known: Tremor, somnolence, impaired motor ability, anterograde amnesia, disturbance in attention, dizziness, headache, dysarthria, depressed levels of consciousness

Eye disorders

Not known: Vision blurred, diplopia, nystagmus

Cardiac disorders

Rare: Bradycardia

Not known: Cardiac failure, cardiac arrest

Vascular disorders

Rare: Hypotension, syncope

Respiratory, thoracic and mediastinal disorders

Not known: Respiratory depression, respiratory arrest, increased bronchial secretion

Gastrointestinal disorders

Not known: Salivary hypersecretion, nausea, vomiting, constipation, diarrhoea, dry mouth

Hepatobiliary disorders

Rare: Jaundice

Skin and subcutaneous tissue disorders

Uncommon: Pruritus, urticarial, rash

Musculoskeletal and connective tissue disorders

Not known: Muscular weakness

Renal and urinary disorders

Rare: Urinary retention

Not known: Urinary incontinence

Reproductive system and breast disorders

Rare: Gynaecomastia, impotence

General disorders and administration site conditions

Common: Fatigue, withdrawal syndrome

Investigations

Not known: Aspartate aminotransferase increased, alanine aminotransferase increased, blood alkaline phosphatase increased.

Description of selected adverse reactions

Psychiatric and paradoxical reactions

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 are 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 Special warnings and precautions for use).

Depression

Pre-existing depression may be unmasked during benzodiazepine use.

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 Special warnings and precautions for use).

Withdrawal symptoms

Upon abrupt discontinuation of diazepam, withdrawal symptoms may occur (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.) 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 medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions (<https://nzphvc.otago.ac.nz/reporting/>).

4.9 Overdose

Symptoms

In every case of overdose with diazepam, the presence of multiple drug intoxication must be considered.

In overdose with diazepam, symptoms such as confusion, somnolence, ataxia, dysarthria, hypotension and muscular weakness may occur. In case of severe overdose, central nervous system depression and respiratory depression can occur. This may lead to cyanosis, unconsciousness, coma and cardiac arrest. Therefore, the patient must be placed under continuous monitoring.

In recovery phase from an overdose with diazepam, agitation has been reported.

Symptoms of overdose can be more pronounced under the concomitant influence of alcohol or other CNS depressants.

Treatment

In early stage of intoxication, gastrointestinal absorption should be reduced by administering activated charcoal.

A clear airway and adequate ventilation must be maintained, especially in unconscious patients.

Further treatment should be symptomatic and supportive. In intensive care unit, special attention should be given to monitoring of cardiovascular and respiratory functions. Patient's heart rate, blood pressure and body temperature should also be closely monitored.

Flumazenil, a benzodiazepine antagonist, may be administered for the reversal of central depressant effects of diazepam. Flumazenil may only be administered under close supervision.

Due to its high level of binding to plasma proteins, and its large volume of distribution, diazepam is poorly removed by forced diuresis or dialysis.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anxiolytics, benzodiazepine derivatives, ATC code: N05BA01

Diazepam is a benzodiazepine tranquilliser that is believed to act by facilitating the synaptic actions of gamma aminobutyric acid (GABA). GABA is one of the major inhibitory neurotransmitters of the

CNS. Diazepam does not act at the same site as GABA, but at a presumably allosterically-linked site, called the benzodiazepine receptor. It is through this site that the anticonvulsant, sedative, skeletal muscle relaxant and amnesic properties of diazepam are mediated.

5.2 Pharmacokinetic properties

Diazepam is readily and completely absorbed from the gastrointestinal tract. Peak plasma concentrations occur in 30 to 60 minutes after administration, but may be further delayed in elderly patients. Diazepam has a biphasic elimination curve, the terminal half-life being 1-2 days. It is extensively protein-bound.

Diazepam is metabolised in the liver and the following active metabolites are produced: desmethyldiazepam, methyloxazepam, oxazepam and temazepam. The metabolites are then eliminated by the kidneys in either their free or conjugated form. The half-life of diazepam is prolonged in patients with kidney or liver disease. Diazepam and its active metabolites show significant accumulation during multiple dosage regimens. Steady state plasma concentrations are attained in 5 days to 2 weeks, as some of its metabolites take several days to weeks to be eliminated.

5.3 Preclinical safety data

None.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose, magnesium stearate, maize starch, quinolone yellow (5 mg only).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30°C. Protect from light.

6.5 Nature and contents of container

PVC/Aluminium foil blister strips: 50 tablets

High density polyethylene bottles: Pack size of 200 and 500 tablets.

Not all pack types or pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MEDICINE SCHEDULE

Controlled Drug C5

8. SPONSOR

Teva Pharma (New Zealand) Limited

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9. DATE OF FIRST APPROVAL

14 May 2009

10. DATE OF REVISION OF THE TEXT

11 May 2022

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.3, 4.4	Additional information to more adequately describe the risks of misuse, abuse, addiction, dependence and withdrawal reactions, as requested by Medsafe.
4.5, 4.6, 4.7, 4.8, 4.9	Updated to fully align with Teva Company Core Safety Information (CCSI).