

# 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 and in patients with a history of drug abuse or dependence.

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.

Amnesia may occur.

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

The dependence potential of the benzodiazepines is low but this increases when high doses are used, especially when given over long periods. This is particularly so in patients with a history of alcoholism or drug abuse or in patients with marked personality disorders. Regular monitoring in such patients is essential, routine repeat prescriptions should be avoided and treatment should be withdrawn gradually. Symptoms such as depression, nervousness, rebound insomnia, irritability, sweating and diarrhoea have reported following abrupt cessation of treatment in patients receiving even normal therapeutic doses for short periods of time.

In rare instances, withdrawal following excessive dosages may produce confusional states, psychotic manifestations and convulsions.

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.

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

Withdrawal symptoms occur with benzodiazepines following normal therapeutic doses given for short periods of time.

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**

There is evidence that tolerance develops to the sedative effects of benzodiazepines.

## **Dependence and Withdrawal**

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. Dependence can occur even with therapeutic doses administered for short periods of time.

Discontinuation of diazepam therapy may result in withdrawal or rebound phenomena. 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.

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.

The diazepam dose should be tapered gradually to minimise the occurrence of withdrawal symptoms.

## **Psychiatric and/or paradoxical reactions**

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.

Diazepam should be discontinued if confusion or agitation occurs.

## **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).

## **Abuse**

Because of a risk of abuse, repeat prescriptions should not be given without medical review.

## **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 cardio-vascular depression (see Section 4.5 Interactions with medicines and other forms of interaction).

## **Risks from Concomitant Use with Opioids**

Concomitant use of benzodiazepines, including Arrow - 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 Arrow - 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 Arrow - 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**

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.

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<sub>A</sub> 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.

Known inhibitors of hepatic enzymes eg. cimetidine and omeprazole, have been shown to reduce the clearance of benzodiazepines and may potentiate their action and known inducers of hepatic enzymes, eg. rifampicin, may increase the clearance of benzodiazepines.

#### **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.

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.

#### **4.7 Effects on ability to drive and use machines**

Sedation, amnesia, impaired concentration and impaired muscle function may adversely affect the ability to drive or to use machines. 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**

Common adverse effects include drowsiness, sedation, unsteadiness and ataxia. These effects occur following single as well as repeated dosage, and may persist into the following day.

The elderly are particularly sensitive to the effects 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.

Other adverse effects are rare and include headache, vertigo, hypotension, gastrointestinal upsets, skin rashes, visual disturbances, changes in libido and urinary retention. Isolated cases of blood dyscrasias and jaundice have also been reported.

Paradoxical reactions such as acute hyperexcitation, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances and stimulation have been reported; should any of these reactions occur, the use of the drug should be discontinued.

The elderly, and patients with impaired renal and/or 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.

#### **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**

When taken alone in overdosage diazepam presents few problems in management. Signs may include drowsiness, ataxia and dysarthria, with coma in severe cases. Treatment is symptomatic. Gastric lavage is useful only if performed soon after ingestion.

The value of dialysis has not been determined. Flumazenil is a specific IV antidote for use in emergency situations. Patients requiring such intervention should be monitored closely in hospital.

When taken with centrally-acting drugs, especially alcohol, the effects of overdosage are likely to be more severe and, in the absence of supportive measures, may prove fatal.

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.

## **6.6 Special precautions for disposal**

No special requirements for disposal.

# **7. MEDICINE SCHEDULE**

Controlled Drug C5

# **8. SPONSOR**

Teva Pharma (New Zealand) Limited

PO Box 128 244

Remuera

Auckland 1541

Telephone: 0800 800 097

# **9. DATE OF FIRST APPROVAL**

14 May 2009

## **10. DATE OF REVISION OF THE TEXT**

12 December 2019

### **SUMMARY TABLE OF CHANGES**

<b>Section changed</b>	<b>Summary of new information</b>
6.1	List of excipients updated.