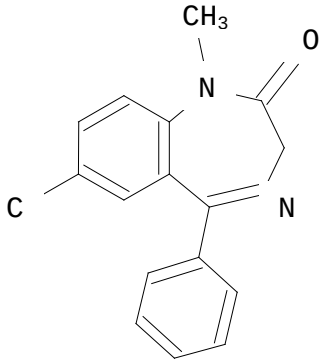
Valpam®

PRODUCT INFORMATION

Name of the medicine

Diazepam. The chemical name for diazepam is 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one. Its structural formula is:



$C_{16}H_{13}ClN_2O$ Molecular weight: 284.74 CAS No.: 439-14-5

Description

Diazepam is a white or almost white, crystalline powder which is odourless or almost odourless. It is very slightly soluble in water, soluble in ethanol (96%); freely soluble in chloroform.

Valpam tablets come in two strengths and contain 2 mg or 5 mg of diazepam. The tablets also contain the following excipients: lactose, maize starch and magnesium stearate. Valpam 5 mg tablets also contain quinoline yellow. The tablets are gluten free.

Pharmacology

Diazepam is a member of the group of benzodiazepines and exhibits anxiolytic, sedative, muscle relaxant and anticonvulsant effects. This is presumed to be the result of facilitating the action in the brain of gamma-aminobutyric acid, a naturally occurring inhibitory transmitter.

Pharmacokinetics

Diazepam is rapidly and completely absorbed from the gastrointestinal tract after oral administration, with peak plasma concentrations occurring 30 to 90 minutes after ingestion. The plasma concentration time curve is biphasic, an initial rapid and extensive distribution phase with a half-life of up to 3 hours, followed by a prolonged terminal elimination phase (half-life 20 to 48 hours). The elimination half-life is 90 hours at age 80 and increased two to three-fold in patients with cirrhosis.

It is metabolised to hydroxy-diazepam (temazepam) and nor-diazepam (t½ approximately 96 hours) and ultimately to oxazepam. Diazepam is 98% protein bound in the plasma, and is excreted mainly (about 70%) in the urine in free form or (predominantly) as conjugated metabolites. The elimination half-life may be prolonged in the newborn, the elderly and patients with hepatic or renal disease and it should be noted that the plasma concentration may take correspondingly longer to reach steady state. Diazepam and its metabolites cross the blood-brain and placental barriers and are also found in breast milk.

Indications

Management of anxiety disorders or for the short-term relief of the symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.

In acute alcohol withdrawal, diazepam may be useful in the symptomatic relief of acute agitation, tremor, impending or acute delirium tremens and hallucinosis.

Diazepam is a useful adjunct for the relief of reflex muscle spasm due to local trauma (injury, inflammation) to muscles, bones and joints. It can also be used to combat spasticity due to upper motor neuron lesions such as cerebral palsy and paraplegia, as well as in athetosis and stiff-man syndrome.

Contraindications

Diazepam is contra-indicated in:

1. Patients with known hypersensitivity to benzodiazepines.

2. Patients with chronic obstructive airways disease with incipient respiratory failure.

3. Patients with severe respiratory insufficiency.

4. Patients with severe hepatic insufficiency.

5. Patients with sleep apnoea syndrome.

6. Patients with myasthenia gravis.

7. Patients with dependence on other substances including alcohol. An exception to the latter is the management of acute withdrawal reactions.

Benzodiazepines are not recommended for the primary treatment of psychotic illness.

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

Precautions

Patients should be advised that their tolerance for alcohol and other CNS depressants will be diminished and that these medications should either be eliminated or given in reduced dosage in the presence of diazepam.

Sedation, amnesia, impaired concentration and impaired muscle function may adversely affect the ability to drive or operate machinery. As with all patients taking CNS-depressant medications, patients receiving diazepam should be warned not to operate dangerous machinery or motor vehicles until it is known that they do not become drowsy or dizzy from diazepam therapy. Abilities may be impaired on the day following use.

Following the prolonged use of diazepam at therapeutic doses, withdrawal from the medication should be gradual. An individualised withdrawal timetable needs to be planned for each patient in whom dependence is known or suspected. Periods from four weeks to four months have been suggested. As with other benzodiazepines, when treatment is suddenly withdrawn, a temporary increase of sleep disturbance can occur after use of diazepam (see Precautions, Dependence).

In general, benzodiazepines should be prescribed for short periods only (e.g. 2 to 4 weeks). Continuous long-term use of diazepam is not recommended. There is evidence that tolerance develops to the sedative effects of benzodiazepines. After as little as one week of therapy withdrawal symptoms can appear following the cessation of recommended doses (e.g. rebound insomnia following cessation of a hypnotic benzodiazepine).

Although hypotension has occurred only rarely, diazepam should be administered with caution to patients in whom a drop in blood pressure might lead to cardiac or cerebral complications. This is particularly important in elderly patients.

Transient amnesia or memory impairment has been reported in association with the use of benzodiazepines.

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

Caution should be used in the treatment of patients with acute narrow-angle glaucoma (because of atropine-like side effects).

Impaired renal/liver function and blood dyscrasias: Patients with impaired renal or hepatic function should use benzodiazepine medication with caution and dosage reduction may be advisable. In rare instances some patients taking benzodiazepines have developed blood dyscrasias, and some have had elevations of liver enzymes. As with other benzodiazepines, periodic blood counts and liver function tests are recommended.

Depression, psychosis and schizophrenia: Diazepam is not recommended as primary therapy in patients with depression or psychosis. In such conditions, psychiatric assessment and supervision are necessary if benzodiazepines are indicated. Benzodiazepines may increase depression in some patients, and may contribute to deterioration in severely disturbed schizophrenics with confusion and withdrawal. Suicidal tendencies may be present or uncovered and protective measures may be required.

Paradoxical reactions such as restlessness, agitation, irritability, aggressiveness, delusion, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects, acute rage, stimulation or excitement may occur; should such reactions occur, diazepam should be discontinued. They are more likely to occur in children and in the elderly.

Geriatric or debilitated patients: Such patients may be particularly susceptible to the sedative effects of benzodiazepines and associated giddiness, ataxia and confusion which may increase the possibility of a fall.

Lower doses should be used for elderly and debilitated patients.

Impaired respiratory function: Caution in the use of diazepam is recommended in patients with respiratory depression. In patients with chronic obstructive pulmonary disease, benzodiazepines can cause increased arterial carbon dioxide tension and decreased arterial oxygen tension. A lower dose is recommended for patients with chronic respiratory insufficiency, due to the risk of respiratory depression.

Epilepsy: When diazepam is administered to persons with convulsive disorders, an increase in the frequency and/or severity of grand mal seizures may occur, necessitating increased anticonvulsant medication. Abrupt withdrawal of benzodiazepines in patients with convulsive disorders may be associated with a temporary increase in the frequency and/or severity of seizures.

Abuse: Extreme caution must be exercised in administering diazepam to individuals with a history of alcohol or drug abuse or those known to be addiction prone or those whose history

suggests they may increase the dosage on their own initiative. It is desirable to limit repeat prescription without adequate medical supervision.

Dependence: The use of benzodiazepines may lead to dependence, as defined by the presence of a withdrawal syndrome on discontinuation of the drug. The risk of dependence increases with dose and duration of treatment. It is more pronounced in patients on long-term therapy and/or high dosage and particularly so in predisposed patients with a history of alcohol or drug abuse. Tolerance, as defined by a need to increase the dose in order to achieve the same therapeutic effect, seldom occurs in patients receiving the recommended doses under medical supervision. Tolerance to sedation may occur with benzodiazepines, especially in those with drug seeking behaviour.

Withdrawal symptoms similar in character to those noted with barbiturates and alcohol have occurred once physical dependence to benzodiazepines has developed or following abrupt discontinuation of benzodiazepines. These symptoms can range from insomnia, anxiety, dysphoria, palpitations, panic attacks, vertigo, myoclonus, akinesia, hypersensitivity to light, sound and touch, abnormal body sensations (e.g. feelings of motion, metallic taste), depersonalisation, derealisation, delusional beliefs, hyperreflexia and loss of short term memory, to a major syndrome which may include convulsions, tremor, abdominal and muscle cramps, confusional states, delirium, hallucinations, hyperthermia, psychosis, vomiting and sweating.

Such manifestations of withdrawal, especially the more serious ones, are more common in those patients who have received excessive doses over a prolonged period. However, withdrawal symptoms have also been reported following abrupt discontinuation of benzodiazepines taken continuously at therapeutic levels. Accordingly, diazepam should be terminated by tapering the dose to minimise occurrence of withdrawal symptoms. Patients should be advised to consult with their physician before either increasing the dose or abruptly discontinuing the medication.

Rebound phenomena have been described in the context of benzodiazepine use. Rebound insomnia and anxiety mean an increase in the severity of these symptoms beyond pre-treatment levels following cessation of benzodiazepines. Rebound phenomena in general possibly reflect re-emergence of pre-existing symptoms combined with withdrawal symptoms described earlier. Some patients prescribed benzodiazepines with very short half-lives (in the order of 2 to 4 hours) may experience relatively mild rebound symptoms in between their regular doses. Withdrawal/rebound symptoms may follow high doses taken for relatively short periods.

Use in pregnancy (Category C)

An increased risk of congenital malformation associated with the use of benzodiazepines during the first trimester of pregnancy has been suggested. Benzodiazepines should be avoided during pregnancy unless there is no safer alternative. Benzodiazepines cross the placenta and may cause hypotonia, respiratory depression and hypothermia in the newborn infant if used in high doses during labour. Continuous treatment during pregnancy and administration of high doses in connection with delivery should be avoided. Withdrawal symptoms in newborn infants have been reported with prolonged use of this class of drugs. Special care must be taken when diazepam is used during labour and delivery, as single high doses may produce irregularities in the foetal heart rate and hypotonia, poor sucking, hypothermia and moderate respiratory depression in the neonate. 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).

Use in lactation

Diazepam is excreted in human breast milk, and may cause drowsiness and feeding difficulties in the infant. Breast-feeding is not recommended in patients receiving diazepam.

Paediatric use

Efficacy and safety of diazepam has not been established in the neonate (30 days or less in age). Prolonged central nervous system depression has been observed in neonates due to inability to

transform the drug. In view of lack of adequate clinical experience chronic oral use is not recommended in children younger than 6 months.

Effect on laboratory tests

Minor EEG changes, usually low voltage fast activity, of no known clinical significance, have been reported with benzodiazepine administration.

Laboratory tests: Diazepam can inhibit binding of thyroxine and liothyronine to their binding proteins resulting in erroneously abnormal values from thyroid function test.

Interactions with other medicines

1. The benzodiazepines, including diazepam, produce additive CNS depressant effects when co-administered with other medications which themselves produce CNS depression, e.g. barbiturates, alcohol, sedatives, anxiolytics, antidepressants including tricyclic antidepressants and non-selective MAO inhibitors, hypnotics, antiepileptic drugs, phenothiazines and other antipsychotics, skeletal muscle relaxants, antihistamines or narcotic analgesics and anaesthetics. Therefore, it should be borne in mind that the effect of these drugs may potentiate or be potentiated by the action of diazepam.

   Concomitant use with alcohol is not recommended due to enhancement of the sedative effect.

2. There is a potentially relevant interaction between diazepam and compounds which inhibit certain hepatic enzymes (particularly cytochrome P_{450}IIIA). Data indicate that these compounds influence the pharmacokinetics of diazepam and may lead to increased and prolonged sedation. Diazepam undergoes oxidative metabolism, and consequently may interact with disulfiram, cimetidine, ketoconazole, fluvoxamine, fluoxetine or omeprazole resulting in increased plasma levels of diazepam. Patients should be observed closely for evidence of enhanced benzodiazepine response during concomitant treatment with either disulfiram or cimetidine; some patients may require a reduction in benzodiazepine dosage.

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

3. Cisapride may lead to a temporary increase in the sedative effects of orally administered benzodiazepines due to faster absorption.

4. The anticholinergic effects of other drugs, including atropine and similar drugs, antihistamines and antidepressants may be potentiated.

5. Interactions have been reported between some benzodiazepines and anticonvulsants, with changes in the serum concentration of the benzodiazepine or anticonvulsant. It is recommended that patients be observed for altered responses when benzodiazepines and anticonvulsants are prescribed together, and that serum level monitoring of the anticonvulsant be performed more frequently.

Adverse effects

More common reactions: Side effects most commonly reported are drowsiness, fatigue, muscle weakness and ataxia. These effects are usually dose related.

Less common reactions: Infrequently encountered effects are amnesia, confusion, depression, constipation, dysarthria, diplopia, gastrointestinal disturbances, headache, hypotension,

incontinence, nausea, changes in libido, changes in salivation, urinary retention, skin reactions such as rash, slurred speech, tremor, vertigo, and blurred vision.

Dizziness has been reported occasionally with diazepam.

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

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.

Very rarely, elevated transaminases and alkaline phosphatase, jaundice as well as cases of cardiac arrest have been reported. Isolated reports of neutropenia have been reported. Periodic blood counts and liver function tests are advisable during long-term therapy.

Chronic use (even at therapeutic doses) of oral diazepam may lead to the development of physical dependence, discontinuation of the therapy may result in withdrawal or rebound phenomena.

Dosage and administration

For maximal beneficial effect, the dosage should be carefully individualised. Dosage may need to be reduced in patients with hepatic or renal disease, as the elimination half-life may be prolonged in this subgroup.

Elderly patients should be given a reduced dose. These patients should be checked regularly at the start of treatment in order to minimise the dosage and/or frequency of administration to prevent overdose due to accumulation.

Usual adult dosage: 5 to 40 mg daily.

Average dosage for ambulatory patients: 2 mg three times daily or 5 mg in the evening and 2 mg once or twice during the day.

Muscle spasm: 10 to 30 mg daily.

Elderly or debilitated patients: 2 mg twice daily or half the usual adult dose.

Children: 6 months to 3 years: 1 to 6 mg daily; 4 to 14 years: 4 to 12 mg daily or calculated from 0.1 to 0.3 mg/kg bodyweight.

Benzodiazepines should not be given to children without careful assessment of the indication: the duration of treatment must be kept to a minimum.

Hospital treatment of tension, excitation, motor unrest: 10 to 15 mg three times daily until the acute symptoms subside.

Overdosage

Symptoms

Overdosage of benzodiazepines is usually manifested by degrees of central nervous system depression ranging from drowsiness to coma. In mild cases, symptoms include drowsiness, mental confusion and lethargy. In more serious cases, symptoms may include ataxia, hypotonia, hypotension, respiratory depression, coma, and very rarely proves fatal.

Treatment

In the management of overdosage with any medication, it should be borne in mind that multiple agents may have been taken.

Following overdosage with oral benzodiazepines, activated charcoal should be given to reduce absorption. General supportive measures are recommended. In the management of overdosage special attention should be paid to the respiratory and cardiovascular functions in intensive care. Hypotension and respiratory depression should be managed according to general principles. Haemoperfusion and haemodialysis are not useful in benzodiazepine intoxication.

The benzodiazepine antagonist flumazenil may be used in hospitalised patients for the reversal of acute benzodiazepine effects. Please consult the flumazenil product information prior to usage.

The use of flumazenil is not recommended in epileptic patients who have been treated with diazepam (or any other benzodiazepine). The reversal of the benzodiazepine effect could induce convulsions in such patients.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

Presentation and storage conditions

Presentation

Valpam 2: Contains 2 mg of diazepam. Round, flat bevel edged, white to off-white tablet engraved with 'DZ' break line '2' on one side and plain on the other side. HDPE bottles with PP child resistant closures of 30, 50, 60, 90, 100* & 200* tablets. PVC/Al blister packs of 30, 50, 60 & 90 tablets.

Valpam 5: Contains 5 mg of diazepam. Round, flat bevel edged light yellow tablet engraved with 'DZ' break line '5' on one side and plain on the other side. HDPE bottles with PP child resistant closures of 30, 50, 60, 90, 100* & 200* tablets. PVC/Al blister packs of 30, 50, 60 & 90 tablets.

* Hospital Use Only

(Note: Not all pack sizes and strengths may be marketed).

Storage conditions

Store below 30°C. Protect from light.

Name and address of the sponsor

Aspen Pharma Pty Ltd
34-36 Chandos Street,
St. Leonards NSW 2065
Australia

Poison schedule of the medicine

S4

Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG)

30 November 2001

Date of most recent amendment

2 September 2014