

Section 3 - Summary of Product Characteristics

Product Summary

1 Trade Name of the Medicinal Product

DIAZEPAM TABLETS BP 2mg

2 Qualitative and Quantitative Composition

Each tablet contains 2mg Diazepam PhEur.

3 Pharmaceutical Form

White uncoated tablets.

Clinical Particulars

4.1 Therapeutic indications

Adults

- 1) The short-term relief (2-4 weeks) only, of anxiety which 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.
- 2) Cerebral palsy.
- 3) Muscle spasm.
- 4) As an adjunct to certain types of epilepsy (*eg* myoclonus).
- 5) Symptomatic treatment of acute alcohol withdrawal.
- 6) As oral premedication for the nervous dental patient.
- 7) For premedication before surgery

Children

- 1) Control of tension and irritability in cerebral spasticity in selected cases
- 2) As an adjunct to the control of muscle spasm in tetanus
- 3) Oral premedication (see section 4.4)

4.2 Posology and method of administration

Posology

As an anxiolytic, the lowest effective dose should be employed; dosage regimes should not exceed beyond 4 weeks and treatment should be gradually withdrawn. Patients who have received benzodiazepines for a long time may require an extended withdrawal period. Long-term chronic use is not recommended.

Adults:

Anxiety states, obsessive-compulsive neuroses, and other psychiatric disorders: 5-30mg daily in divided doses.

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

Cerebral palsy: 5-60mg daily in divided doses.

Upper motor neuron spasticity: 5-60mg daily in divided doses.

Muscle spasm of varied aetiology, fibrositis, cervical spondylosis: 5-15mg daily in divided doses.

Adjunct to the management of some types of epilepsy: 2-60 mg daily in divided doses.

Alcohol withdrawal: 5-20mg, repeated if necessary in 2 to 4 hours.

Oral premedication in dental patients: 5mg the night before, 5mg on waking and 5mg two hours before the appointment.

Oral Premedication before surgery: 5mg-20mg.

Children:

Alternative presentations of diazepam are recommended for paediatric usage in order to obtain suitable doses of less than 5mg.

Spastic children with minimal brain damage: 5-40mg daily in divided doses.

Oral Premedication before surgery (see section 4.4): 2mg-10mg

Elderly and debilitated patients:

Doses should be half the above recommended doses.

Renal and hepatic impairment (see section 4.4):

The use of diazepam in hepatic impairment may precipitate coma, therefore the dose should be reduced or an alternative drug considered. In severe renal impairment the dose should be reduced.

Method of Administration

For oral administration.

4.3 Contraindications

- Known hypersensitivity to benzodiazepines and any other ingredients in diazepam tablets
- Phobic or obsessional states; chronic psychosis (paradoxical reactions may occur)
- Acute pulmonary insufficiency; respiratory depression (ventilatory failure may be exacerbated)
- Acute narrow angle glaucoma (due to anticholinergic effects of diazepam)
- Myasthenia gravis (condition may be exacerbated)
- Sleep apnoea (condition may be exacerbated)
- Severe hepatic insufficiency (elimination half-life of diazepam may be prolonged)
- Acute porphyria
- 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.

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.

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

Use of diazepam may lead to the development of physical and psychic dependence. The risk of dependence increases with the dose and duration of treatment, and in patients with a history of alcoholism and drug abuse.

Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms (see Section 4.8 Undesirable Effects).

Rebound insomnia and anxiety: a transient syndrome whereby the symptoms that led to treatment with diazepam may recur in an enhanced form on withdrawal of treatment. It may be accompanied by other reactions including mood changes, anxiety or sleep disturbances and restlessness. Since the risk of withdrawal phenomena/rebound phenomena is greater after abrupt discontinuation of treatment, it is recommended that the dosage is decreased gradually.

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

Some 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).
- Amnesia - diazepam may induce anterograde amnesia. The condition occurs most often several hours after ingesting the product and therefore to reduce the risk patients should ensure that they will be able to have uninterrupted sleep of 7-8 hours.
- In cases of loss of bereavement, psychological adjustment may be inhibited by benzodiazepines.
- Diazepam should be used with caution in patients with a history of alcohol or drug abuse as these are patients predisposed to habituation and dependence.
- Hypoalbuminaemia may predispose patient to higher incidence of sedative side effects.
- Extreme caution should be used in prescribing diazepam to patients with personality disorders.
- Benzodiazepines should not be used in patients with severe hepatic insufficiency as they may precipitate encephalopathy.
- Cerebral sensitivity is increased in severe renal failure, therefore lower doses should be used (see section 4.2).
- Hypnotics should be avoided in the elderly who are at risk of becoming ataxic and confused and so liable to fall and injure themselves. If, based on clinical need, a decision to treat is nevertheless taken, treatment should be initiated at a lower dose (see section 4.2).
- Caution should be exercised when using diazepam peri-operatively in children, as effects and timing of response may be unreliable and paradoxical effects may occur.

4.5 Interaction with other medicinal products and other forms of interaction

The following drug interactions with diazepam should be considered:

- Increased sedative effects are likely when diazepam is used concurrently with antipsychotics, narcotic analgesics, antidepressants, hypnotics, general anaesthetics, antihistamines, lofexidine, nabilone, disulfiram, muscle relaxants, alcohol.
In case of narcotic analgesics, enhancement of euphoria may occur, resulting in an increase in dependence.
- Cimetidine, oestrogen-containing contraceptives, disulfiram, erythromycin may inhibit hepatic metabolism of diazepam.
- Ulcer-healing-drugs: Omeprazole and cimetidine may increase the plasma concentration of diazepam.
- Antibacterials: Isoniazid may inhibit diazepam metabolism. Rifampicin may increase the metabolism of diazepam.
- Antivirals: Concomitant use of diazepam with amrenavir and ritonavir should be avoided, as there is an increased risk of prolonged sedation and respiratory depression.
- Antiepileptic drugs: Pharmacokinetic studies on potential interactions between diazepam and antiepileptic drugs have produced conflicting results. Both depression and elevation of drug levels, as well as no change, have been reported. Plasma concentrations of zotepine are increased. Therefore, special care should be taken in adjusting the dose in the initial stages of treatment.
- Alcohol: The sedative effects may be enhanced when diazepam is used in combination with alcohol. Concomitant intake with alcohol should be avoided.
- Antihypertensives, diuretics, nitrates: Enhanced hypotensive effects may occur. Enhanced sedative effect with alpha blockers or moxonidine.
- Dopaminergics: Concurrent use with benzodiazepines may decrease the therapeutic effects of levodopa.
- Baclofen or tizanidine (enhanced sedative effect)
- Antacids (concurrent use may delay absorption of diazepam).

4.6 Pregnancy and lactation

The safety of diazepam has not been evaluated in humans and therefore its use should be avoided, especially in the first and third trimester.

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.

Since benzodiazepines are found in the breast milk, benzodiazepines should not be given to breast feeding mothers.

4.7 Effects on ability to drive and use machines

Sedation, amnesia and impaired muscular function may adversely affect the ability to drive or use machines. If insufficient sleep occurs, the likelihood of impaired alertness may be increased (see also Interactions).

Impaired function and sedation may occur the following morning and for several days after.

4.8 Undesirable effects

- Common adverse effects include drowsiness, sedation, unsteadiness and ataxia. These effects are dose-related and may persist into the following day even after a single dose.
- 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 effects of central 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.
- *Withdrawal effects on abrupt cessation of treatment* - Depression, nervousness, rebound insomnia, irritability, sweating and diarrhoea have been reported following abrupt cessation of treatment. In rare cases, withdrawal following excessive dosages may produce confusional states, psychotic manifestations and convulsions.
- As with all benzodiazepines, withdrawal may be associated with physiological and psychological symptoms including depression.
- Abnormal psychological reactions to benzodiazepines have been reported. Behavioral adverse effects include paradoxical aggressive outbursts, excitement, confusion and the uncovering of depression with suicidal tendencies.
- Adverse effects are rare and include allergic reaction (skin rash or itching), headache, vertigo, hypotension, gastrointestinal upsets, dystonic effects, visual disturbances, libido fluctuations, urinary retention, blood dyscrasias and jaundice.

4.9 Overdose

The symptoms of diazepam overdose are mainly an intensification of the therapeutic effects (ataxia, drowsiness, dysarthria, sedation, muscle weakness, profound sleep) or paradoxical excitation. In most cases only observation of vital functions is required.

Extreme overdosage may lead to coma, areflexia, cardiorespiratory depression and apnoea, requiring appropriate countermeasures (ventilation, cardiovascular support).

Consider activated charcoal (50g for an adult, 1g/kg for a child) in adults who have taken more than 100mg or or children who have taken more than 1mg/kg within one hour, provided they are not too drowsy. Supportive measures are indicated depending on the patient's clinical state.

Benzodiazepines are not significantly removed from the body by dialysis.

Anexate (flumazenil) is a specific IV antidote for use in emergency situations providing the overdose is not with mixed drugs. Patients requiring such intervention should be monitored closely in hospital.

Occasionally a respirator may be required but generally few problems are encountered, although behavioral changes are likely in children.

If excitation occurs, barbiturates should not be used.

Effects of overdose are more severe when taken with centrally-acting drugs, especially alcohol, and in the absence of supportive measures, may prove fatal.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: N05B A01

Diazepam is a benzodiazepine tranquilliser with anticonvulsant, sedative, muscle relaxant and amnesic properties.

5.2 Pharmacokinetic properties

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

Diazepam is extensively metabolised in the liver and, in addition to desmethyldiazepam, its active metabolites include oxazepam and temazepam. It is excreted in the urine, mainly in the form of its metabolites, either free or in conjugated form. Diazepam is very extensively bound to plasma proteins.

The plasma half-life of diazepam is prolonged in neonates, in the elderly, and in patients with kidney or liver disease. In addition to crossing the blood-brain barrier, diazepam and its metabolites also cross the placental barrier and are excreted in breast milk.

5.3 Preclinical safety data

Not applicable.

Pharmaceutical Particulars

6.1 List of excipients

Also contains: lactose, magnesium stearate, maize starch, stearic acid.

6.2 Incompatibilities

None known.

6.3 Shelf-life

Shelf-life

Three years from the date of manufacture.

Shelf-life after dilution/reconstitution

Not applicable.

Shelf-life after first opening

Not applicable.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

The product containers are rigid injection moulded polypropylene or injection blow-moulded polyethylene containers and snap-on polyethylene lids; in case any supply difficulties should arise the alternative is amber glass containers with screw caps.

The product may also be supplied in blister packs in cartons:

a) Carton: Printed carton manufactured from white folding box board.

b) Blister pack: (i) 250µm white rigid PVC. (ii) Surface printed 20µm hard temper aluminium foil with 5-6g/M² PVC and PVdC compatible heat seal lacquer on the reverse side.

The product may be contained in blister packs which enhances security of the pack increasing resistance to deliberate contamination, pilfering, etc.

Pack size: 28, 30, 50, 56, 60, 84, 90, 100, 112, 120, 168, 180, 250, 500, 1000.

Product may also be supplied in bulk packs, for reassembly purposes only, in polybags contained in tins, skillets or polybuckets filled with suitable cushioning material. Bulk packs are included for *temporary* storage of the finished product before final packaging into the proposed marketing containers.

Maximum size of bulk packs: 50,000.

6.6 Instructions for use/handling

Not applicable.

Administrative Data

7 Marketing Authorisation Holder

Actavis UK Limited
(Trading style: Actavis)

Whiddon Valley
BARNSTAPLE
N Devon EX32 8NS

8 Marketing Authorisation Number

PL 0142/0087

9 Date of First Authorisation/Renewal of Authorisation

15.7.77
(Renewed: 15.7.82; 15.7.87; 3.9.92)

10 Date of (Partial) Revision of the Text

May 2007