

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Diazepam 10 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg of diazepam. For excipients see 6.1.

3. PHARMACEUTICAL FORM

Tablet.

Blue, flat, bevel edged tablets, Engraved "Berk 10" with a breakline on reverse or "10" with a breakline on reverse.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

Diazepam is indicated for the short-term relief only (2-4 weeks) 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. The use of benzodiazepines to treat short-term "mild" anxiety is considered to be inappropriate and unsuitable.

Diazepam may be used for the short-term treatment of insomnia only when it is severe, disabling or subjecting the individual to extreme distress.

Diazepam is also indicated for muscle spasm and premedication.

4.2 Posology and method of administration

As an anxiolytic, the lowest effective dose which can control the symptoms should be employed; dosage regimes should not exceed beyond 4 weeks and treatment with benzodiazepines should always be gradually withdrawn. Patients who have received benzodiazepines for a long time may require an extended withdrawal period during

which the doses are reduced. Long-term chronic use is not recommended. Long-term chronic use is not recommended; treatment should be as short as possible. The patient should be reassessed regularly and the need for continued treatment evaluated, especially if the patient is symptom free. It should not exceed 2-3 months for anxiety and 4 weeks for insomnia, including the tapering off period. Extension beyond these periods should not take place without re-evaluation of the situation.

Anxiety States: Adults

Usual dose of 2 mg three times daily.

Severe anxiety states: 15-30 mg daily in divided doses.

Insomnia associated with anxiety: Adults

5 - 15 mg before retiring. The maximum dose should not be exceeded.

Conditions associated with muscle spasm:

Spastic children with minimal brain damage: 2-40 mg daily in divided doses.

Cerebral palsy of adults, particularly associated with athetoid movements: 2-60 mg daily in divided doses.

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

Muscle spasm of varied aetiology: fibrositis, cervical spondylosis: 2-15 mg daily in divided doses.

Premedication:

Adults: 5-20 mg

Children: 2-10 mg

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

Elderly or debilitated patients:

Doses should not exceed half the dose recommended for adults.

These patients should be monitored regularly at the start of treatment in order to minimise if necessary, the dose or frequency of administration to prevent overdose due to accumulation.

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

Benzodiazepines should not be used for phobic or obsessional states. They should not be used as monotherapy in patients with depression or those with anxiety and depression as suicide may be precipitated in such patients.. They should not be used for the treatment of chronic psychosis, hyperkinesia (paradoxical reactions may occur). Amnesia may occur.

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 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.

Benzodiazepines are also contraindicated in patients with known sensitivity to benzodiazepines and any of the excipients, severe or acute pulmonary insufficiency, severe hepatic insufficiency (elimination half-life of diazepam may be prolonged), acute porphyria, myasthenia gravis (condition may be exacerbated), sleep apnoea syndrome (condition may be exacerbated), respiratory depression, acute or chronic severe respiratory insufficiency (ventilatory failure may be exacerbated).

Planning a pregnancy (see section 4.6).

Pregnancy (unless there are compelling reasons – see section 4.6).

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 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. Patients with marked personality disorders, a history of alcoholism or drug abuse are most susceptible. Monitoring of patients at regular intervals is essential, routine repeat prescriptions should be avoided and treatment should be withdrawn gradually.

Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms (see Section 4.8 Undesirable Effects). These may consist of headache, muscle pain, tension, extreme anxiety, confusion, restlessness and irritability. In severe cases derealization, depersonalisation, numbness and tingling of the extremities, hyperacusis, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures may occur. .

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 . This may occur on withdrawal of treatment and may be accompanied by other reactions including mood changes, anxiety, sleep disturbances and restlessness.

Since the risk of withdrawal phenomena and rebound phenomena is greater after abrupt discontinuation of treatment, it is recommended that the dosage be decreased gradually.

As sudden discontinuation of benzodiazepines may result in convulsions, particular care should be taken in patients with epilepsy, other patients who have had a history of seizures or in alcohol dependants.

Tolerance - Limits of tolerance in patients with organic cerebral changes (particularly arteriosclerosis) or cardio-respiratory 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 benzodiazepines may develop after repeated use for a few weeks.

Alcohol should be avoided during treatment with diazepam (additive CNS depression).

Amnesia - Benzodiazepines may induce anterograde amnesia. Amnesic effects may be associated with inappropriate behaviour. Anterograde amnesia may occur using therapeutic dosages, the risk increasing at higher dosages. 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. Anterograde amnesia may occur using therapeutic doses, the risk increases with higher doses.

In cases of loss or 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.

Hypo-albuminaemia 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.

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).

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 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.

Paradoxical reactions such as restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects are known to occur when using benzodiazepines. Should this occur, the use of the drug should be discontinued. They are more likely to occur in children and in the elderly.

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

4.5 Interaction with other medicinal products and other forms of interaction

Not recommended

Alcohol

Concomitant use with alcohol is not recommended due to enhancement of the sedative effect. This affects the ability to drive and use machinery.

Sodium oxybate

Avoid concomitant use (enhanced 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 enhancement of the central depressive effect **or** sedative effects of diazepam are likely to be intensified by concomitant administration with centrally-acting drugs such as neuroleptics, antipsychotics, anxiolytics/sedatives, tranquillisers, antidepressants, hypnotics, anti-convulsants, analgesics, narcotic analgesics, anaesthetics, barbiturates and sedative antihistamines. The elderly may require special supervision.

Narcotic analgesics

In the case of narcotic analgesics, enhancement of euphoria may also occur leading to an increase in psychic dependence. The elderly require supervision.

Anti-epileptic 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.

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

Other drugs enhancing the sedative effect of diazepam

Cisapride, lofexidine, nabilone, disulfiram and the muscle-relaxants - baclofen and tizanidine. Cisapride 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):

Known inhibitors of hepatic enzymes : e.g cimetidine: isoniazid: erythromycin: omeprazole: esomeprazole, fluvoxamine and fluoxetine have been shown to reduce the clearance of benzodiazepines and may potentiate their action .

Itraconazole, ketoconazole, and to a lesser extent fluconazole and voriconazole are potent inhibitors of the cytochrome P450 isoenzyme CYP3A4 and may increase plasma levels of benzodiazepine. The effects of benzodiazepine may be increased and prolonged by concomitant use. A dose reduction of the benzodiazepine may be required.

known inducers of hepatic enzymes e.g. rifampicin, may increase the clearance of benzodiazepines.

Antihypertensives, vasodilators & diuretics:

Enhanced hypotensive effect with ACE inhibitors, alpha-blockers, angiotensin-II receptor antagonists, calcium channel blockers, adrenergic neurone blockers, beta-blockers, moxonidine, nitrates, hydralazine, minoxidil, sodium nitroprusside and diuretics. Enhanced sedative effect with alpha-blockers or moxonidine.

Dopaminergics

Possible antagonism of the effect of levodopa.

Antacids

Concurrent use may delay absorption of diazepam

Zidovudine

Increased zidovudine clearance by diazepam.

Oestrogen-containing contraceptives

Possible inhibition of hepatic metabolism of diazepam.

Theophylline

Increases metabolism of diazepam which possibly reduces the effect.

Caffeine

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

Grapefruit juice

Inhibition of CYP3A4 may increase the plasma concentration of diazepam (possible increased sedation and amnesia). This interaction may be 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

There is no evidence as to drug safety in human pregnancy, nor is there evidence from animal work that it is free from hazard. Do not use during pregnancy, especially during the first and last trimesters, unless there is a compelling reason. 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.

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 irregularities in foetal heart rate have been reported, effects 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 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, 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

Common adverse effects include drowsiness, sedation, amnesia, impaired muscular function, unsteadiness and ataxia may adversely effect the ability to drive or use machines, These are dose related and may persist into the following day, even after a single dose. 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.

Performance and alertness may be impaired during the first week of administration.

Patients should be warned that effects on the central nervous system may persist into the day after administration even after a single dose.

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.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

The medicine is likely to affect your ability to drive,

- Do not drive until you know how the medicine affects you
- It is an offence to drive while under the influence of this medicine

However, you would not be committing an offence (called 'statutory defence') if:

- The medicine has been prescribed to treat a medical or dental problem and
- You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
- It was not affecting your ability to drive safely.

4.8 Undesirable effects

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 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. 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 disorders

Allergic reactions (skin rash or itching) occur rarely.

Central and peripheral nervous disorders

Sedation, unsteadiness, ataxia is common (these effects are dose-related and may persist into the following day even after a single dose), light-headedness, headache, vertigo, dystonic effects occur rarely. Impaired motor ability, dizziness, tremor, dysarthria, slurred speech.

Vision disorders

Blurred vision. Diplopia

Visual disturbances occur rarely.

Psychiatric disorders

Libido fluctuations (increase or decrease in libido) occur rarely. Depression. Benzodiazepines may induce 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, the uncovering of depression with suicidal tendencies and dependence (see section 4.4). Other adverse behavioural effects are known to occur when using benzodiazepines (see 4.4 Special warnings and precautions for use). Abuse of benzodiazepines has been reported.

Gastro-intestinal system disorders

Hypersalivation, gastrointestinal disturbances, constipation, nausea, dry mouth.

Gastrointestinal upsets occur rarely.

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

Fatigue most commonly reported.

Anaphylaxis.

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.

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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Symptoms

Benzodiazepines commonly cause drowsiness, ataxia, dysarthria and nystagmus. Coma, hypotension and respiratory depression occasionally occur but are seldom serious if these drugs are taken alone. Coma usually lasts only a few hours but in elderly people it may be more protracted and cyclical. Benzodiazepine respiratory depressant effects are more serious in patients with severe chronic respiratory disease.

Benzodiazepines potentiate the effects of other central nervous system depressants, including alcohol.

Management

Consider activated charcoal in adults or children who have taken more than 1 mg/kg within 1 hour, provided they are not too drowsy. Gastric lavage is unnecessary if these drugs have been taken alone. Patients who are asymptomatic at four hours are unlikely to develop symptoms. Institute supportive measures as indicated by the patient's clinical state.

If CNS depression is severe consider the use of flumazenil (Anexate), a benzodiazepine antagonist. This should rarely be required. It has a short half-life (about an hour) and should NOT BE USED IN MIXED OVERDOSE OR AS A "DIAGNOSTIC" TEST. It is contraindicated in the presence of drugs that reduce seizure threshold (e.g. tricyclic antidepressants).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: N05B A01 (anxiolytics, benzodiazepine derivatives)

Diazepam is a benzodiazepine tranquilliser with anticonvulsant, sedative, hypnotic, muscle relaxant and amnesic properties. These are believed to act on specific receptors close to the GABA receptor where they facilitate its effects. The exact physiological role of GABA is not understood although it is known to be an inhibitory transmitter which dampens neuronal activity in the brain. Benzodiazepines, such as diazepam, bind to receptors in various regions of the brain and spinal cord. This binding increases the inhibitory effects of gamma-aminobutyric acid (GABA). GABA's functions include CNS involvement in sleep induction. Also involved in the control of hypnosis, memory, anxiety, epilepsy and neuronal excitability.

Diazepam is a long-acting benzodiazepine due to the formation of the long-lasting, pharmacologically active metabolite nordiazepam. Repeated doses may lead to accumulation of drug metabolites. The elderly and those with renal and/or hepatic impairment will be particularly susceptible to the adverse effects.

5.2 Pharmacokinetic properties

Absorption: Diazepam is readily and completely absorbed from the GI tract. Peak plasma concentrations occurring within about 30-90 minutes of oral administration, a steady plasma concentration is reached after 5-6 days and is directly related to dose.

Distribution: Diazepam has a mean volume of distribution of 0.7 L/Kg (Range 0.18-1.30L/Kg). Diazepam crosses the blood-brain barrier and is highly lipid soluble, this causes the initial effects to decrease rapidly as it is redistributed into fat deposits and tissues. The drug is highly plasma protein-bound in the range 98-100%. Diazepam and its metabolites also enter breast milk and cross the placenta freely, this may lead to accumulation in the infant or foetus.

Metabolism: Diazepam is extensively metabolised in the liver and, in addition to desmethyldiazepam, its active metabolites include oxazepam and temazepam. Diazepam has a half-life of between 20-42 hours (Mean 30 hours). 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. The plasma half-life of diazepam is prolonged in neonates, in the elderly, and in patients with kidney or liver disease.

Elimination: It is excreted in the urine, mainly in the form of its metabolites, either free or in conjugated form.

5.3. Pre-clinical Safety Data

Preclinical information has not been included because the safety profile of diazepam has been established after many years of clinical use. Please refer to section 4.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

The tablets contain:
Lactose monohydrate
Powdered cellulose
Maize starch
Pregelatinised maize starch
Magnesium stearate (E572)
Indigo carmine (E132).

6.2. Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4. Special Precautions for Storage

Store at or below 25°C. Protect from moisture and light.

6.5 Nature and contents of container

Blister packs in strips of 7, 10, 14, 21, 28, 30, 56, 60, 84, 90, 100, 110, 112, 120, 150, 160 and 168.

Not all pack sizes may be marketed.

6.6. Instructions for Use, Handling and Disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

TEVA UK Limited
Brampton Road, Hampden Park,
Eastbourne, East Sussex, BN22 9AG

8 MARKETING AUTHORISATION NUMBER(S)

PL 0289/0166

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

24/09/1996

10 DATE OF REVISION OF THE TEXT

19/05/2015