SUMMARY OF PRODUCT CHARACTERISTICS OF COZEPAM 5 MG TABLET

1. Name of the medicinal product

Cozepam-5 Tablets

2. Qualitative and quantitative composition

Each tablet contains 5 mg of Diazepam.

3. Pharmaceutical form

Uncoated tablet

4. Clinical particulars

4.1 Therapeutic indications

Anxiety

Insomnia

Benzodiazepines are only indicated when the disorder is severe, disabling or subjecting the individual to extreme distress.

4.2 Posology and method of administration

Anxiety

Treatment should be as short as possible. The patient should be reassessed regularly and the need for continued treatment should be evaluated, especially in case the patient is symptom free. The overall duration of treatment generally should not be more than 8-12 weeks, including a tapering off process.

Insomnia

Treatment should be as short as possible. Generally the duration of treatment varies from a few days to two weeks with a maximum, including tapering off process of four weeks.

Anxiety states:

Severe anxiety states: 15 to 30mg.

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

4.3 Contraindications

Known hypersensitivity to benzodiazepines or any of the ingredients

Severe or acute respiratory insufficiency/ depression

Sleep apnoea syndrome

Severe hepatic insufficiency

Diazepam should not be used in phobic or obsessional states, nor be used alone in the treatment of depression or anxiety associated with depression due to the risk of suicide being precipitated in this patient group. Diazepam should not be used for the primary treatment of psychotic illness. In common with other benzodiazepines the use of diazepam may be associated with amnesia and diazepam should not be used in cases of loss or bereavement as psychological adjustments may be inhibited.

4.4 Special warnings and precautions for use

Diazepam should be used with caution in patients with renal or hepatic dysfunction, chronic pulmonary insufficiency, porphyria, myasthenia gravis, coma, a known history of drug or alcohol abuse, or organic brain changes, particularly arteriosclerosis.

Diazepam may enhance the effects of other CNS depressants; their concurrent use should be avoided.

Tolerance

Some loss of efficacy to the hypnotic effects of benzodiazepines may develop after repeated use for a few weeks.

Dependence

Use of benzodiazepines may lead to the development of physical and psychic dependence upon these products. This should be considered when treating patients for more than a few days. The risk of dependence increases with dose and duration of treatment; it is also greater in patients with a history of alcohol or drug abuse. It is low when limited to short term use.

Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms.

Rebound insomnia and anxiety: a transient syndrome whereby the symptoms that led to treatment with a benzodiazepine recur in an enhanced form, may occur 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.

Duration of treatment

The duration of treatment should be as short as possible depending on the indication, but should not exceed 4 weeks for insomnia and eight to twelve weeks in case of anxiety., including tapering off process. Extension beyond these periods should not take place without re-evaluation of the situation.

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 minimising anxiety over such symptoms should they occur while the medicinal product is being discontinued.

There are indications that, in the case of benzodiazepines with a short duration of action, withdrawal phenomena can become manifest within the dosage interval, especially when the dosage is high.

When benzodiazepines with a long duration of action are being used it is important to warn against changing to a benzodiazepine with a short duration of action, as withdrawal symptoms may develop.

Amnesia

Benzodiazepines 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 an uninterrupted sleep of seven to eight hours.

Psychiatric and 'paradoxical' reactions

Reactions like 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, use of the drug should be discontinued.

They are more likely to occur in children and the elderly.

Specific patient groups

Benzodiazepines should not be given to children without careful assessment of the need to do so; the duration of treatment must be kept to a minimum. Elderly and debilitated patients are more prone to the CNS effects of benzodiazepines and, therefore, should be given a reduced dose . A lower dose is also recommended for patients with chronic respiratory insufficiency due to the risk of respiratory depression. Benzodiazepines are not indicated to treat patients with severe hepatic insufficiency as they may precipitate encephalopathy.

Benzodiazepines should be used with extreme caution in patients with a history of alcohol or drug abuse.

As with other benzodiazepines, extreme caution should be used if prescribing diazepam for patients with personality disorders. The disinhibiting effects of benzodiazepines may be manifested as the precipitation of suicide in patients who show aggressive behaviour towards self and others.

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

Alcohol: Concomitant intake with alcohol 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.

Anaesthetics and narcotic analgesics: Enhancement of the central depressive effect may occur, with enhanced sedation or respiratory and cardiovascular depression. In the case of narcotic analgesics, enhancement of euphoria may also occur leading to an increase in psychic dependence.

Antibacterials: Agents that interfere with metabolism by hepatic enzymes (e.g. erythromycin and isoniazid) may reduce the clearance of benzodiazepines and potentiate their action. Known inducers of hepatic enzymes, for example, rifampicin, may increase the clearance of benzodiazepines.

Antidepressants: Enhanced sedation or respiratory and cardiovascular depression. Diazepam plasma levels increased by concomitant fluvoxamine.

Antiepileptics: Enhanced sedation or respiratory and cardiovascular depression. Known inducers of hepatic enzymes, for example carbamazepine, and phenytoin, may increase the clearance of benzodiazepines. Serum phenytoin levels may rise, fall or remain unaltered. In addition, phenytoin may cause diazepam serum levels to fall. Concomitant sodium valproate may increase serum levels of diazepam, with associated drowsiness.

Antihistamines: Enhanced sedation or respiratory and cardiovascular depression with sedative antihistamines.

Antihypertensives: Enhanced hypotensive effect, enhanced sedative effect with alpha blockers and possibly moxonidine.

Antipsychotics: Enhanced sedation or respiratory and cardiovascular depression. Increased plasma concentrations of zotepine. Severe hypotension, collapse, respiratory depression, potentially fatal respiratory arrest and unconsciousness have been reported in a few patients on benzodiazepines and clozapine. Caution is advised when initiating clozapine therapy in patients taking benzodiazepines.

Antivirals: Amprenavir, and ritonavir have been shown to reduce the clearance benzodiazepines and may potentiate their actions, with risk of extreme sedation and respiratory depression – avoid concomitant use.

Anxiolytics: Enhanced sedation or respiratory and cardiovascular depression with other anxiolytics.

Digoxin: Reduced clearance of digoxin

Disulfiram: has been shown to reduce clearance and may potentiate actions of benzodiazepines.

Dopaminergic agents: diazepam may cause inhibition of levodopa.

Hypnotics: Enhanced sedation or respiratory and cardiovascular depression.

Lofexidine: Enhanced sedation or respiratory and cardiovascular depression

Muscle relaxants: Increased CNS depressant effects with baclofen and tizanidine.

Nabilone: Enhanced sedation or respiratory and cardiovascular depression.

Nicotine: Diazepam metabolism is accelerated by smoking.

Oral contraceptives: Reduce the clearance of benzodiazepines and may potentiate their actions.

Sedatives: Enhanced sedation or respiratory and cardiovascular depression.

Theophylline: Diazepam metabolism is accelerated by theophylline.

Ulcer-healing drugs: Cimetidine, and omeprazole may reduce the clearance of benzodiazepines and potentiate their actions

4.6 Pregnancy and lactation

There is no evidence regarding the safety of diazepam in pregnancy. Diazepam tablets should not be used in pregnancy, especially during the first and third trimesters, unless the benefit is considered to outweigh the risk.

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

Patients treated with diazepam tablets should not drive or operate machinery as sedation, amnesia, impaired concentration and impaired muscular function may adversely affect their ability. If insufficient sleep duration occurs, the likelihood of impaired alertness may be increased.

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 of 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

Cardiovascular: Hypotension, particularly with high dosage, bradycardia, chest pain.

CNS: Elderly or debilitated patients are particularly susceptible to the CNS effects of benzodiazepines. It is recommended that dosage be limited to the smallest effective dose and increased gradually, if necessary, to decrease the possibility of development of ataxia, dizziness, and oversedation, which may lead to falls and other accidents.

Disorders of the eye: Visual disturbances

Gastrointestinal: Dry mouth gastrointestinal disturbances

General: Fatigue and a hangover effect.

Haematological: Blood dyscrasias

Hepatic: Raised liver enzymes, jaundice.

Immunological: Hypersensitivity reactions, including anaphylaxis, are rare.

Neurological: Headaches, confusion, slurred speech, tremor, reduced alertness. Anterograde amnesia may occur using therapeutic dosages, the risk increasing at higher dosages . Amnestic effects may be associated with inappropriate behaviour.

Psychiatric disorders: Numbed emotions. Pre-existing depression may be unmasked during benzodiazepine use. Paradoxical reactions (including aggressive behaviour, hostility, disinhibition, euphoria, excitation, irritability, increased anxiety, and insomnia) are known to occur with benzodiazepines. They may be quite severe with this product. They are more likely to occur in children and the elderly.

Reproductive disorders: Changes in libido, gynaecomastia.

Respiratory disorders: Rarely, respiratory depression and apnoea, particularly with high dosage.

Urinary: Urinary retention, incontinence.

Withdrawal symptoms: 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.

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.

Abuse of benzodiazepines has been reported.

4.9 Overdose

Features

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

Extreme overdosage may lead to coma, areflexia, cardio-respiratory depression and apnoea, requiring appropriate countermeasures (ventilation, cardiovascular support). Benzodiazepine respiratory depressant effects are more serious in patients with severe chronic obstructive airways disease. Severe effects in overdose also include rhabdomyolysis and hypothermia.

Management

Maintain a clear airway and adequate ventilation.

Consider activated charcoal (50g for an adult, 1g/kg for a child) in adults who have taken more than 100mg or children who have taken more than 1mg/kg within one hour, provided they are not too drowsy.

Monitoring level of consciousness, respiratory rate, pulse oximetry and blood pressure in symptomatic patients.

Consider arterial blood gas analysis in patients who have a reduced level of consciousness (GCS < 8; AVPU scale P or U) or have reduced oxygen saturations on pulse oximetry.

Correct hypotension by raising the foot of the bed and by giving an appropriate fluid challenge. Where hypotension is thought mainly due to decreased systemic vascular resistance, drugs with alpha-adrenergic activity such as noradrenaline or high dose dopamine (10-30 micrograms/kg/min) may be beneficial. The dose of inotrope should be titrated against blood pressure.

If severe hypotension persists despite the above measures, then central venous pressure monitoring should be considered.

Supportive measures are indicated depending on the patient's clinical state.

Benzodiazepines are not significantly removed from the body by dialysis.

5. Pharmacological properties

5.1 Pharmacodynamic properties

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

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). GABAs functions include CNS involvement in sleep induction. Also involved in the control of hypnosis, memory, anxiety, epilepsy and neuronal excitability.

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 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 Diazepam is very extensively bound to plasma proteins (98-99%). Diazepam and its metabolites also enters breast milk and crosses the placenta freely, this may lead to accumulation in the infant or foetus.

Biotransformation

Diazepam is extensively metabolised in the liver and, in addition to desmethyldiazepam, its active metabolites include oxazepam and temazepam. 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 Preclinical safety data

Not applicable.

6. Pharmaceutical particulars

6.1 List of excipients

Maize starch BP

Lactose BP

Potassium sorbate

Tartrazine yellow water soluble

Magnesium stearate BP

Aerosil BP

Purified water BP

6.2 Incompatibilities

None known

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 30°C in a dry place in the absence of light.

6.5 Nature and contents of container

PVC /Aluminium foil, Packs of 28 Tablets in a carton

6.6 Special precautions for disposal and other handling

Not applicable.

7 Registrant

Cosmos Limited

8 Manufacturer

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