SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DIAZEM 5 mg Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains:

Active substance:

Diazepam 5.0 mg

Excipient(s):

Lactose monohydrate 44.0 mg

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsule

White opaque body, light green opaque cap, white, odorless, homogeneous-looking powder in hard gelatin capsules (No: 3).

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

It is used in the short-term symptomatic treatment of neurotic anxiety, in agitation, tremor, delirium tremens and hallucinations in acute alcohol withdrawal, in reflex spasms of skeletal muscles due to local pathology, in spasticity due to upper motor neurons (cerebral paralysis and paraplegia), in some types of epilepsy, in the control of tension and irritability due to cerebral spasticity in children, in the control of muscle spasm in tetanus, in oral premedication, in premedication before surgery.

4.2. Posology and method of administration

Posology, frequency and duration of administration:

The dose should be adjusted according to the patient for best results.

Treatment is usually started with the lowest dose that can control symptoms. Diazem should be used as an anxiolytic in doses of 5-30 mg 2 or 3 times a day.

In acute alcohol withdrawal: 5-20 mg daily at intervals of 2 to 4 hours if necessary,

As a sedative hypnotic: should be used at bedtime, 5-15 mg per day.

Method of administration:

For oral use.

Additional information on special populations:

Renal / hepatic impairment:

Diazem metabolites are excreted in significant amounts through the kidneys and the risk of toxic reactions may be high in patients with impaired renal function. Diazem should therefore be used with caution in patients with kidney disease.

Diazem is contraindicated in severe hepatic impairment. (see section 4.3 Contraindications)

Paediatric population:

In pediatric patients under 6 months of age, efficacy and safety are unknown.

Geriatric population:

In elderly patients, it is recommended to use the lowest effective dose of diazepam to prevent ataxia or excessive sedation. If the medicine is tolerated, the dose can be increased gradually. It is recommended to use half the adult dose.

4.3. Contraindications

Diazem should not be used in the following conditions:

- People with hypersensitivity to benzodiazepines and any of the substances in the composition of the preparation
- Infants under 6 months of age
- In acute alcohol intoxication
- Mental depression (benzodiazepines increase depression when used alone)
- Myasthenia gravis
- Narrow-angle glaucoma
- In cases of psychosis
- In severe liver impairment
- In severe respiratory impairment
- Transient respiratory impairment during sleep
- Acute porphyria

4.4. Special warnings and precautions for use

The duration of treatment should be as short as possible depending on the indication and should not exceed 4 weeks. Treatment should not be continued after 4 weeks without reassessment of the patient's condition. In cases where long-term treatment is necessary, regular review of the patient's requirements is recommended.

When treatment is initiated, it should be fully explained to the patient that treatment will be of limited duration and that the dose will be gradually reduced. The patient can thus be made aware of the possibility of a rebound event with discontinuation of diazepam treatment, minimizing symptoms such as anxiety that may occur.

WARNING MAY CAUSE DEPENDENCY.

Avoid taking diazem with alcoholic beverages, it may cause drowsiness.

Cross sensitization:

If there is sensitivity to one of the benzodiazepines, this is also the case for diazepam.

General warnings:

It should be used with caution in patients with a predisposition to drug dependence.

As with other anticonvulsant drugs, when diazepam is used as adjunctive therapy for convulsive disorders, increased frequency of convulsions or Grand mal seizures may require an increase in the dose of standard anticonvulsant drugs.

In epileptic patients, abrupt discontinuation of diazepam may increase the frequency and severity of grandmal seizures.

Due to the depressing effect of diazepam on the central nervous system, patients should be warned against alcohol and drugs that depress the central nervous system during diazepam treatment.

Caution should be exercised in patients with impaired hepatic and renal function. Sedative effects may be increased in hypoalbuminemia. They may increase breathing difficulties in patients with chronic obstructive pulmonary disease.

Pediatric and geriatric use:

Particularly young patients and elderly patients are more sensitive to the effects of benzodiazepines on the central nervous system. Results in prolonged central nervous system depression in newborns.

Physical and psychological dependence:

In sudden discontinuation of diazepam, symptoms such as convulsions, tremor, abdominal and muscle cramps, vomiting and sweating may occur, similar to sudden discontinuation of substances such as barbiturates and alcohol. Therefore, in any long-term treatment, the medication should be reduced gradually.

Each Diazem capsule contains 44.0 mg lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption, should not take this medicinal product.

The capsule structure of this product contains tartrazine. It may cause allergic reactions.

4.5. Interaction with other medicinal products and other forms of interaction

Concomitant use with antacids prolongs the absorption time.

Carbamazepine may lower serum levels of both drugs, reducing their effects.

Omeprazole and cimetidine inhibit microsomal oxidation of diazepam. The effect may be exacerbated.

May interact with other central nervous system depressants. The effect intensifies.

Metabolism of diazepam may decrease with concomitant use of isoniazid.

Additive synergy with neuromuscular junction blockers (curare-like drugs, muscle relaxants) is observed.

Rifampin may increase the elimination of diazepam.

Combination with alcohol may cause drowsiness.

The risk of developing withdrawal syndrome increases with the combination of benzodiazepines prescribed as anxiolytics or hypnotics.

Concomitant use with benzodiazepines may reduce the therapeutic effects of dopaminergic drugs (levodopa).

Itraconazole, ketoconazole and fluconazole are inhibitors of the cytochrome P450 isoenzyme CYP3A4 and may increase plasma levels of benzodiazepines. The effects of benzodiazepines may be increased and prolonged with concomitant use. It may be necessary to reduce the benzodiazepine dose.

Theophylline reduces the effect of diazepam by increasing its metabolism.

Grapefruit juice inhibits CYP3A4 and may prolong sedation and amnesia by increasing the plasma concentration of diazepam. Although this interaction is of little importance in healthy individuals, other factors such as old age or liver cirrhosis may increase the risk of adverse effects.

4.6. Pregnancy and lactation

General advice

Pregnancy category is D.

Women of childbearing potential / Birth control (Contraception)

Since its use in the first trimester of pregnancy increases the risk of congenital malformations, it is not recommended for women of childbearing potential and an appropriate contraceptive method is recommended.

Pregnancy

Diazepam has harmful pharmacological effects on pregnancy and/or fetus/newborn.

Diazem should not be used during pregnancy unless necessary (the conditions for this should be specified).

Diazepam easily crosses the placenta. Its use in the first trimester of pregnancy increases the risk of congenital malformations. Therefore, the risk/benefit ratio should be carefully evaluated during pregnancy. Meanwhile, since there is rarely an urgent need for benzodiazepines, the use of diazepam should generally be avoided during pregnancy.

Lactation

Since diazepam and N-desmethyldiazepam are easily excreted in breast milk, breastfeeding women should avoid using this medicine during this period.

Reproductivity/Fertility

In studies in mice and rats, a dose of 80 mg/kg/day diazepam had no adverse effects on fertility or viability of offspring. (approximately 13 times the maximum recommended human dose in mg/m²).

4.7. Effects on ability to drive and use machines

Like many drugs that affect the central nervous system, diazepam can cause a decrease in attention and wakefulness, which can have dangerous consequences for drivers of vehicles and machine operators.

4.8. Undesirable effects

Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), unknown (cannot be estimated from the available data).

Psychiatric disorders

Common: Sleepiness, weakness, fatigue, drowsiness and ataxia.

Rare: Confusion, depression, altered libido. Paradoxical reactions such as acute hyperexcitation states, anxiety, hallucinations, increased muscle spasticity, insomnia, irritability, sleep disturbances and arousal have been reported. If these effects are observed, the use of the drug should be discontinued.

Nervous system disorders

Rare: Headache, dizziness, tremor, tongue wandering when speaking (dysarthria)

Eye disorders

Rare: Double vision, blurred vision

Vascular disorders

Rare: Hypotension

Gastrointestinal disorders

Rare: Constipation, nausea, changes in salivation

Hepatobiliary disorders

Rare: Jaundice

Skin and subcutaneous tissue disorders

Rare: Skin rashes

Renal and urinary disorders

Rare: Urinary retention, incontinence

Investigations

Rare: Since neutropenia and jaundice have been reported in long-term treatment, periodic blood counts and liver function tests are recommended.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization 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 national reporting system.

4.9. Overdose

Symptoms:

At high doses, somnolence, mental confusion, inability to stand, difficulty in speech, bradycardia, respiratory weakness and extreme weakness may be observed.

Precautions:

If the patient is conscious, emesis is achieved mechanically or with emetics. Gastric lavage can be performed if the patient is unconscious. Respiration, pulse and blood pressure should be monitored. Serum can be applied. Hypotension can be controlled with I.V. norepinephrine or metaraminol. Barbiturates should not be used if excitation occurs. Dialysis is of little importance.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Benzodiazepine derivatives

ATC code: N05BA01

Diazepam interacts with specific benzodiazepine receptors in the central nervous system, maximizing pre- and post-synaptic inhibition of GABA at various synapses to exert its effect. There are various studies showing that inhibition in 5-HT and noradrenergic neurons may be responsible for anxiolytic and sedative effects. Cortical benzodiazepine receptors are suggested to be responsible for anticonvulsant effects.

5.2. Pharmacokinetic properties

General properties

Absorption: The majority (>90%) of diazepam is absorbed following oral administration. When diazepam is administered with moderately fatty meals, absorption of diazepam is reduced or delayed.

Distribution: Diazepam and its metabolites are highly bound to plasma proteins. They also cross the blood-brain and placental barrier. Diazepam and its metabolites are present in breast milk at approximately 1:10 the concentration of maternal plasma. (3-9 days postpartum). The deviation in the concentration-time curve profile of the drug is biphasic after oral administration.

Biotransformation: Diazepam is biotransformed in the liver to active metabolites such as N-desmethyl diazepam, temazepam and oxazepam.

Elimination: The elimination half-life of diazepam is quite long. Considering that the elimination half-life of diazepam is 20-70 hours, N-desmethyl diazepam 30-200 hours, temazepam 10-20 hours and oxazepam 5-15 hours, it should be taken into consideration that the drug will cumulate in a short time in chronic use. It is not considered a good hypnotic as it can leave a residual effect. It is excreted in the urine in free or conjugated form as its main metabolites.

Linearity/nonlinearity: No data are available.

5.3. Preclinical safety data

The active substance contained in the preparation is a substance that has been used in clinical practice for many years. Studies on it have been completed. Any adverse effects that may be observed in relation to their use are listed in the relevant sections. (see 4.4. Special warnings and precautions for use, 4.5. Interaction with other medicinal products and other forms of interaction, 4.8. Undesirable effects, 4.9. Overdose).

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lactose monohydrate

Starch

Magnesium stearate

Indigotine

Titanium dioxide

Tartrazine

6.2. Incompatibilities

For information on drug interactions, see section 4.5. Interaction with other medicinal products and other forms of interaction

Diazepam is not incompatible with the excipients used.

6.3. Shelf life

48 months

6.4. Special precautions for storage

Store at room temperature below 30°C protected from light.

6.5. Nature and contents of container

Blisters of 25 capsules covered with transparent PVC foil on one side and printed aluminum foil on the other side.

Each cardboard box contains 25 or 50 capsules.

6.6. Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER

83/48

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORIZATION

Date of first authorization: 14.09.1966

Renewal of the authorization: 01.05.2003

10. DATE OF REVISION OF THE TEXT