SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DİAPAM 10 mg/2 mL I.M./I.V. Solution for Injection
Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2mL ampoule:
Active Ingredient:
Diazepam…….10 mg

Excipients:
Propylene glycol…….800 mg
Ethyl alcohol…….. 200 mg
Sodium benzoate……....60 mg
Benzoic acid……...40 mg
Benzyl alcohol……30 mg

For the full list of excipients, see 6.1.

3. PHARMACEUTICAL FORM

Solution for Injection.
Almost colorless to pale yellow clear solution with characteristic odour.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

DİAPAM is used

- In moderate and severe psychoneurotic reactions
- In the syndrome of alcohol abstinence
- To relieve muscle spasms
- Before endoscopic procedures
- In status epilepticus and recurrent severe convulsive seizures
- In preoperative medication

4.2. Posology and method of administration

Posology /administration frequency and duration

- In moderate psychoneurotic reactions:

  It is given as 2-5 mg IM or IV only in cases manifested by tension-anxiety or depressive symptoms, agitation, restlessness and psychophysiological disturbances and this dose is repeated every 3-4 hours if necessary.

- In severe psychoneurotic reactions:

In cases of anxiety, worry and agitation with or without depressive symptoms, 5-10 mg is given IM or IV. This dose is repeated every 3-4 hours if necessary.

- In the syndrome of alcohol abstinence

For the prevention of acute agitation, tremor, delirium tremens and hallucinations and for the relief of symptoms after the formation of the table, it is given as 10 mg by IM or IV route. This dose can be repeated every 3-4 hours if necessary.

- To relieve muscle spasms

First, 5-10 mg is given IM or IV, and this dose can be repeated every 3-4 hours if necessary. Higher doses may be required in tetanus.

- Before endoscopic procedures

Immediately before the procedure, the IV route is given very slowly, until the desired sedation is achieved. Usually 10 mg is sufficient, but if narcotic drugs are not used together, this dose can be increased to 20 mg. In cases where IV administration is not possible, 5-10 mg should be given by IM route 30 minutes before endoscopy.
If narcotics are used together, the dose of these drugs should be reduced by at least 1/3.

- In status epilepticus and recurrent severe convulsive seizures

IV administration is preferred, but if this is not possible, it can also be administered by IM. IV administration should be done very slowly. Initially, 5-10 mg is given. This dose can be repeated every 10-15 minutes if necessary, but the total dose given should not exceed 30 mg. If necessary, the treatment can be repeated every 2-3 hours, but it should be kept in mind that active metabolites of diazepam may be present in the organism. People with cardiovascular disorders and chronic lung diseases should be treated with extreme caution.

- In preoperative medication

If anxiety and acute stress are present prior to surgical interventions, 5-15 mg given IM or IV 30 minutes before surgery.

Route of administration:
Diazem is for intravenous or intramuscular administration.

Additional information on special populations:
Renal/ Hepatic impairment:
It should be used with caution in patients with hepatic and renal dysfunction.

Pediatric population:

- In tetanus:

For children aged 2-5: 1-2 mg IM or IV (to be given over 3 minutes) is given. This dose can be repeated every 3-4 hours.

For children over 5 years old: 5-10 mg IM or IV (to be given over 3 minutes) is given. This dose can be repeated every 3-4 hours.

- In status epilepticus and recurrent severe convulsive seizures:

0.2 – 0.3 mg/kg IV (or IM) or 1 mg per year of life.

Geriatric population:

Caution should be exercised when using DİAPAM in this patient population. It is appropriate to use half the adult dose.

4.3. Contraindications

DİAPAM is contraindicated in the following conditions.

- In people with hypersensitivity to benzodiazepines and to any of the substances included in the composition of the preparation
- for babies under 6 months of age
- In acute alcohol intoxication
- Mental depression (benzodiazepines increase depression when used alone)
- In Myasthenia gravis
- In narrow-angle glaucoma
- In cases of psychosis
- In severe liver failure
- In severe respiratory failure
- Temporary respiratory failure in sleep
- Acute porphyria

4.4. Special warnings and precautions for use

Except in emergency cases, a second person should always be present next to the patient during intravenous administration of diazepam, and patients should remain under medical supervision for at least an hour after the injection. It is recommended not to drive or use machinery for 24 hours.

Intramuscular injection of diazepam may lead to an increase in serum creatinine phosphokinase activity within 12 and 24 hours.

Absorption of diazepam may vary in intramuscular injection, especially in the gluteal muscles, so this route should be used when intravenous administration is not possible.

Elderly patients with impaired renal and/or hepatic function may be sensitive to the undesirable effects of diazepam. Therefore, a dose reduction may be necessary.

Extreme caution should be exercised when administering diazepam injection to patients with the possibility of respiratory depression or apnea and limited lung reserve.
It should be used with caution in patients with drug or alcohol dependence and arteriosclerosis. Diazepam injection should be administered with caution in patients with low blood pressure, as it may cause cardiovascular or cerebrovascular complications.

Avoid using diazepam together with alcoholic beverages, it may cause drowsiness.

Cross-sensitivity:
If there is sensitivity to one of the benzodiazepines, it is also the case for diazepam.

General warnings:
It should be used with caution in patients predisposed to drug dependence.
As with other anticonvulsant drugs, diazepam; When used as adjunctive therapy in convulsive disorders, increased frequency of convulsions or Grand mal seizures may require an increase in the dose of standard anticonvulsant medication.

Sudden discontinuation of diazepam in epileptic patients may increase the frequency and severity of grand mal 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.

It should be used with caution in those with impaired liver and kidney function. In hypoalbuminemia, sedative effects may increase. They may increase breathing difficulties in those with chronic obstructive pulmonary disease.

Pediatric and geriatric use:
Especially young patients and elderly patients are more sensitive to the effects of benzodiazepines on the central nervous system. It causes long-term central nervous system depression in newborns.

Physical and psychological dependence:
Symptoms such as convulsions, tremor, abdominal and muscle cramps, vomiting and sweating can be seen in the abrupt discontinuation of diazepam, similar to the abrupt discontinuation of substances such as barbiturates and alcohol. Therefore, in all types of long-term treatment, the drug should be gradually reduced.

- DİAPAM ampoules contain propylene glycol. Therefore, it can cause alcohol-like symptoms.
- This medicinal product contains ethanol (alcohol) in 12.07% by volume; for example,

up to 200 mg per dose, equivalent to 5.05 ml beer per dose, equivalent to 2.1 mL wine per dose.

- It can be harmful for those with alcohol dependence. It should be taken into account by pregnant or lactating women, children and patients at high risk, such as liver disease or epilepsy.
- This medicinal product contains less than 1 mmol (23 mg) of sodium per 2 mL; that is, it is considered essentially sodium-free.
- DİAPAM contains 40 mg of benzoic acid in 2 mL. Therefore, it can increase the risk of jaundice in newborn babies.
- DİAPAM contains 30 mg of benzyl alcohol in 2 mL. It should not be applied to premature babies and newborns. It can cause toxic reactions and anaphylactoid reactions in infants and children up to 3 years of age.

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

Concomitant use with antacids may prolong the absorption time.
Carbamazepine can reduce the serum levels of both drugs, reduce the effects.
Cimetidine inhibits microsomal oxidation of diazepam. The effect can be exacerbated.
It may interact with other central nervous system depressants. The effect is exacerbated.
With concomitant use of isoniazid, the metabolization of diazepam may decrease.
Additive synergy can be seen with neuromuscular junction blockers (curare-like drugs, muscle relaxants).
Rifampin may increase the metabolization of diazepam.
Concomitant use with alcohol may cause drowsiness.
The risk of developing withdrawal syndrome increases with the combination of benzodiazepines prescribed anxiolytically or hypnotically.
Concomitant use of benzodiazepines with dopaminergic drugs (levodopa) may reduce their therapeutic effect.
As itraconazole, ketoconazole and fluconazole are inhibitors of cytochrome P450 isoenzyme CYP3A4, they can increase the plasma levels of benzodiazepines. With simultaneous use, the effects of benzodiazepines may increase and prolong. It may be necessary to reduce the dose of benzodiazepines.
Theophylline increases the metabolism of diazepam, reducing its effect.
Grapefruit juice inhibits CYP3A4 and may increase diazepam plasma concentration, prolonging sedation and amnesia. Although this interaction is of little significance 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: D

Women of childbearing potential / contraception
Since the risk of congenital malformations will increase with its use in the first trimester of pregnancy, its use is not recommended for women with childbearing potential, and it is recommended to apply an appropriate contraceptive method.

Pregnancy
Diazepam has harmful pharmacological effects on pregnancy and/or fetus/newborn.
Diazem should not be used during pregnancy unless necessary (conditions for this should be specified). Diazepam easily passes into the placenta. Congenital with use in the first trimester of pregnancy the risk of malformations increases. Therefore, the risk/benefit ratio should be carefully evaluated during pregnancy. Meanwhile, since benzodiazepines are rarely needed urgently, diazepam use should be avoided in general during pregnancy.

Lactation period
Meanwhile, since benzodiazepines are rarely needed urgently, diazepam use should be avoided in general during pregnancy.

Reproductive ability / Fertility
In studies conducted in mice and rats, a dose of 80 mg/kg/day of diazepam did not have any adverse effects on fertility or the ability of offspring to live. (approximately 13 times the maximum recommended human dose in mg/m^2).

4.7. Effects on ability to drive and use machines
Like many drugs that act on the central nervous system, diazepam can have dangerous consequences for vehicle drivers and machine operators, as it can lead to a decrease in attention and alertness.

4.8. Undesirable effects
Very common (≥1/10); common (≥1/100 to < 1 /10); uncommon (≥1/1000 and <1/100); rare (≥1/10.000 and <1/1000); very rare (< 1/10.000), unknown (cannot be estimated from the available data).

Blood and lymphatic system diseases
Unknown : Neutropenia

Psychiatric diseases
Common : Drowsiness, weakness, exhaustion
Rare : Paradoxical reactions such as mental confusion, mental depression, difficulty falling asleep, excitation, nervousness or irritability

Nervous system diseases
Rare : Headache, dizziness, twitching of the tongue when speaking (dysarthria)

Eye diseases
Rare : Blurred vision or other visual changes

Gastrointestinal diseases
Rare : Constipation, vomiting, nausea

Hepato-bilier diseases
Rare : Jaundice

Skin and subcutaneous tissue diseases
Rare : Skin rashes and itching

Reporting of the side effects:
If you get any side effects not listed in this leaflet, talk to your doctor or pharmacist. You can also report side effects directly to your doctor or pharmacist. You can also report side effects directly to your country's related health authority. By reporting side effects, you can help provide more information on the safety of this medicine.

4.9. Overdose and treatment

Symptoms
In high doses, drowsiness, mental confusion, inability to stand, difficulty speaking, bradycardia, weakening of breathing, extreme weakness may occur.

Precautions
If the patient is conscious, emesis is achieved mechanically or with emetics. If the patient is unconscious, gastric lavage can be performed. Breathing, pulse and blood pressure should be observed. Serum can be administered. Hypotension can be controlled with IV norepinephrine or metaraminol. If excitation occurs, barbiturates should not be used. 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 the pre- and post-synaptic inhibition of GABA at various synapses, resulting in an effect. There are several studies showing that inhibition in 5-HT and noradrenergic neurons may

be responsible for anxiolytic and sedative effects. It has been suggested that cortical benzodiazepine receptors may be responsible for the anticonvulsant effects.

5.2. Pharmacokinetic Properties

General properties

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

Distribution: Diazepam and its metabolites are highly bound to plasma proteins. In addition, they cross the blood-brain and placental barrier. Diazepam and its metabolites are found in breast milk at approximately 1:10 concentrations 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 is 30-200 hours, temazepam is 10-20 hours, and oxazepam is 5-15 hours, it should be taken into account that the drug will cumulate in a short time in chronic use. It is not considered a good hypnotic as it can have residual effects. It is excreted in the urine in the form of its basic metabolites, in free or conjugated form.

Linearity/non-linearity:
No data available.

5.3. Pre-clinical safety data

"Diazepam", the active substance contained in DİAPAM, has been used in Turkey and various countries of the world for many years, and all information about it is contained in books with standard monographs and vademecum information. Negative effects that can be seen with their use 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 and treatment).

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Propylene glycol
Ethyl alcohol
Sodium benzoate

Benzoic acid
Benzyl alcohol
Water for injection

6.2. Incompatibilities
Diazepam injection should not be mixed with other drugs or IV fluids and should not normally be diluted except when given slowly in large intravenous infusions of normal saline or dextrose. No more than 40 mg of diazepam should be added to 500 mL of infusion solution. The solution should be freshly prepared and used within six hours.

6.3. Shelf Life
24 months

6.4. Special precautions for storage
Store at room temperature below 25°C, protect from light.

6.5. Nature and contents of container
Ringed 2 mL amber ampoules made of Type I glass
Each carton box contains 10, 50 and 100 pcs of 2 mL ampoules.

6.6. Destruction of the residual materials human medicinal product and other special precautions
Unused products or waste materials should be disposed of in accordance with the "Medical Waste Control Regulation" and "Packaging and Packaging Waste Control Regulation".

7. MARKETING AUTHORIZATION HOLDER
Osel İlaç San. Ve Tic. A.Ş.
Akbaba Mah. Maraş Cad. No.:52 34820
Beykoz / İSTANBUL
Phone: 0(216) 320 45 50
Fax: 0(216) 320 41 45

8. MARKETING AUTHORIZATION NUMBER
191/40

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
First authorization date: 31.05.1999
Renewal date: 28.04.2005

10. DATE OF REVISION OF THE TEXT