SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DIAZEM 10 mg/2 ml Solution for IM/IV Injection
Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2 ml ampoule contains;

Active substance:

Diazepam 10 mg

Excipients with known effect:

Propylene glycol 828 mg
Ethyl alcohol 170.8 mg
Sodium benzoate 96 mg
Benzoic acid 3.7 mg
Benzyl alcohol 31.4 mg
Hydrochloric acid pH: 6.2-7

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Almost colorless to light yellow color and clear solution with a characteristic odor.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Adults

Diazepam is an anxiolytic, anticonvulsant and central muscle relaxant. Diazepam is used to relieve anxiety in severe acute anxiety or agitation, to provide sedation, and to calm agitation due to delirium tremens.

Diazepam is used to treat acute muscle spasms and tetanus.

It is used for acute convulsions, including status epilepticus, as well as convulsions due to poisoning and febrile convulsions, as an aid during endoscopy, in dentistry, surgery, radiology. It is used for cardiac catheterization, cardioversion, to relieve preoperative anxiety, to provide sedation, to provide light anesthesia, and to provide anterograde amnesia.

Pediatric patients

DIAZEM 10 mg/2 ml Solution for IM/IV Injection is indicated:

- In the treatment of status epilepticus, post-poisoning convulsions and febrile convulsions
- In the treatment of tetanus
- In preoperative medication or as premedication

The suitability of treatment with DIAZEM 10 mg/2 ml Solution for IM/IV Injection in pediatric patients may need to be evaluated on a case-by-case basis (see section 4.2).

General

DIAZEM contains propylene glycol and ethyl alcohol. This should be taken into consideration when parenteral benzodiazepines are indicated, particularly when used in high volumes (continuous infusion of high doses to treat tetanus or status epilepticus) and/or in patients at risk of developing propylene glycol toxicity (see section 4.4).

4.2. Posology and method of administration

Posology/frequency and duration of administration:

Adults

Severe acute anxiety or agitation:
It may be given by IV or IM injection of 10 mg, repeated at intervals of not less than 4 hours.

Delirium tremens:
It can be administered at doses of 10 to 20 mg by IM or IV route.
Higher doses may be administered depending on the severity of symptoms.

Acute muscle spasm:
It may be given by IV or IM injection of 10 mg, repeated at intervals of not less than 4 hours.

Tetanus:
It should be administered initially IV, at a dose of 0.1 – 0.3 mg per kilogram of body weight, repeated at 1 – 4 hour intervals. Continuous IV infusion can also be administered at a dose of 3–10 mg per kilogram of body weight every 24 hours. The dose chosen should be related to the severity of the case, with higher doses being used in extremely severe cases.

In status epilepticus and convulsions due to poisoning:
10-20 mg IV or IM repeated after 30-60 minutes if necessary.
If medically necessary, this may be followed by slow intravenous infusion (the maximum dose should be 3 mg per kilogram of body weight over 24 hours).

Preoperative medication or premedication:
It should be administered at a dose of 0.2 mg per kilogram of body weight. The usual adult dose is 10 to 20 mg, but higher doses may be required based on clinical response.

In elderly or weak (frail) patients:
The dose should not exceed half the normal recommended dose.

Hepatic impairment:
The dose of DIAZEM may need to be reduced in patients with chronic liver disease. When DIAZEM is administered at doses of 0.603 mg per kilogram body weight per day (50 mg/kg/day propylene glycol equivalent) and above, medical monitoring is required in patients with liver dysfunction (see section 4.4).

Renal impairment:
There is no clinically significant change in the half-life of diazepam in renal impairment and generally no dose adjustment is required. When DIAZEM is given at doses of 0.603 mg per kilogram body weight per day (equivalent to 50 mg/kg/day propylene glycol) and above, medical monitoring is required in patients with impaired renal function (see section 4.4).

Cardiorespiratory failure:
A lower dose is recommended in patients with chronic respiratory failure due to the risk of respiratory depression.

Pediatric patients
DIAZEM contains propylene glycol and ethyl alcohol (see section 4.4). The European Medicines Agency (EMA) has recommended daily exposure limits for the excipient propylene glycol in the following pediatric populations:

Population	Propylene glycol exposure limit recommended by EMA
Newborn	1 mg/kg/day propylene glycol (equivalent to diazepam administration at a dose of 12.07 micrograms/kg/day)
Infants and toddlers ≥ 1 month and < 5 years	50 mg/kg/day propylene glycol (equivalent to diazepam administration at a dose of 0.603 mg/kg/day)
Children aged 5 years and above	500 mg/kg/day propylene glycol (equivalent to 6.03 mg/kg/day of Diazepam)

Treatment with DIAZEM at the doses recommended for pediatric patients in the following indications may correspond to a propylene glycol dose that may exceed the relevant EMA exposure limit. In such a case, the decision to use DIAZEM should be made on a case-by-case basis and after careful consideration of the potential benefits and risks of treatment (see section 4.4).

Status epilepticus, convulsions due to poisoning, febrile convulsions:
By intravenous injection:

Pediatric patients	Recommended dose
Newborn	300 – 400 micrograms/kg, followed by 300 – 400 micrograms/kg after 10 minutes if necessary. Each injection will be administered over 3 – 5 minutes.
Children between 1 month and 11 years old:	300 - 400 micrograms/kg (maximum 10 mg per dose), followed by a further injection of 300 - 400 micrograms/kg after 10 minutes if necessary. Each injection will be administered over 3 – 5 minutes.
Children aged 12-17 years	10 mg, followed by further 10 mg after 10 minutes if necessary. Each injection will be administered over 3 – 5 minutes.

Tetanus:
By intravenous injection:
It should be administered at a dose of 100-300 micrograms per kilogram every 1 - 4 hours, taking into account body weight.

By intravenous infusion:
It will be administered within 24 hours, with a dose of 3 - 10 mg per kilogram, taking into account body weight, adjusted according to response.

Preoperative medication or premedication:
It should be administered at a dose of 0.2 mg per kilogram of body weight. It should be injected slowly (0.5 ml per minute).

Method of administration
DIAZEM can be administered by IV injection, IM injection, or IV infusion. Absorption of diazepam from IM injection may be variable, particularly for the gluteal muscles. Therefore, the IM route of administration should only be used if IV administration is not possible.

Dilution
DIAZEM should not be mixed with other drugs or IV fluids and should not normally be diluted except when administered slowly in large volume intravenous infusions with 0.9% sodium chloride solution and 5% dextrose solution.

In compatibility studies conducted with 0.9% sodium chloride solution and 5% dextrose solution, it was shown that the solutions obtained by diluting at a concentration of approximately 0.1 mg/ml were compatible for 24 hours at room conditions.

In cases where administration by IV infusion is deemed necessary, it is recommended to mix "DIAZEM 10 mg/2 ml Solution for IM/IV Injection" with at least 200 ml of 0.9% sodium chloride infusion solution or 5% dextrose infusion solution and use it immediately. Solutions to be administered via IV infusion should be diluted and administered in glass bottles.

Intravenous use
IMPORTANT: To reduce the possibility of side effects during intravenous administration, it should be injected slowly (1 ml of solution per minute). It is recommended that the patient remain on his back for at least one hour after the administration. Except in emergencies, a second person should always be present during intravenous use and resuscitation facilities should always be available.

Intravenous injection may be associated with local reactions resulting in thrombophlebitis and venous thrombosis. To minimize the possibility of these effects, intravenous injections of diazepam should be administered into a large antecubital fossa vein.

Duration of treatment
The duration of treatment should be as short as possible to minimize the potential for the development of potential adverse effects of diazepam (e.g., potential for dependence and associated withdrawal effects, potential for interaction with other central nervous system depressants), as well as adverse effects associated with its excipients propylene glycol and ethyl alcohol (see section 4.4). Parenteral DIAZEM is intended for short-term use in cases of acute clinical need. When the clinical situation is suitable for oral use, parenteral therapy should be switched to oral therapy.

Medical supervision
It is recommended that patients remain under medical supervision for at least one hour after the time of injection. They should always be accompanied by a responsible adult and warned not to drive or operate machinery for more than 24 hours.

Depending on the dose of DIAZEM administered, increased medical monitoring may be required in populations at risk of developing propylene glycol toxicity - see recommendations for use in patients with renal or hepatic impairment and in pediatric patients (Posology).
See also section 4.4.

4.3. Contraindications
DIAZEM should not be used in the following conditions:

- In individuals with hypersensitivity to benzodiazepines or any ingredients contained in composition of the preparation (see section 6.1)
- Phobic or obsessive states; chronic psychosis, hyperkinesia (paradoxical reactions may occur)

- Acute pulmonary insufficiency, respiratory depression, acute or chronic severe respiratory failure may get worse.

- In sleep apnea syndrome (the condition may worsen)
- Significant neuromuscular respiratory weakness, including unstable myasthenia gravis (may worsen)
- In severe hepatic impairment (elimination half-life of diazepam may be prolonged)
- Acute porphyria
- If you are planning a pregnancy (see section 4.6)
- Pregnancy (unless there are compelling reasons) (see section 4.6)

DIAZEM should not be used alone in the treatment of depression or anxiety associated with depression due to the risk of suicide.

4.4. Special warnings and precautions for use

Intramuscular administration

IM use of DIAZEM injection may lead to an increase in serum creatine phosphokinase activity, reaching a maximum level 12 to 24 hours after injection. This fact should be taken into account in the differential diagnosis of myocardial infarction.

Propylene glycol

DIAZEM contains propylene glycol (414 mg per 1 mL) and ethyl alcohol (85.4 mg per 1 mL) – see also Ethyl alcohol content. Various adverse effects have been reported with high doses or prolonged use of propylene glycol, including hyperosmolality, lactic acidosis; renal dysfunction (acute tubular necrosis), acute renal failure; cardiotoxicity (arrhythmia, hypotension); central nervous system disorders (depression, coma, seizures); respiratory depression, dyspnea; hepatic dysfunction; hemolytic reaction (intravascular hemolysis) and hemoglobinuria; or multisystem organ dysfunction. Adverse events are generally reversible following discontinuation of propylene glycol and, in more severe cases, following hemodialysis.

Propylene glycol safety thresholds by population:

- *Newborns:*

In newborns, a safety threshold of 1 mg/kg/day for the excipient propylene glycol has been set by the European Medicines Agency (corresponding to a diazepam dose of 12.07 micrograms/kg/day). Exceeding this threshold may result in serious adverse events in this population when administered concomitantly with any substrate for alcohol dehydrogenase (such as ethyl alcohol).

- *Infants and children under 5 years of age*

In infants and children under 5 years of age, a safety threshold of 50 mg/kg/day has been set by the European Medicines Agency for the excipient propylene glycol (corresponding to a diazepam dose of 0.603 mg/kg/day). Co-administration of propylene glycol with any alcohol dehydrogenase substrate (such as ethyl alcohol) at or above this safety threshold may result in adverse effects in this population.

- *Children aged 5 years and above, and adults*

In children aged 5 years and above and in adults, a safety threshold of 500 mg/kg/day for the excipient propylene glycol has been set by the European Medicines Agency (corresponding to a diazepam dose of 6.03 mg/kg/day).

- *Patients with hepatic or renal impairment*

Various side effects attributable to propylene glycol have been reported, including renal dysfunction (acute tubular necrosis), acute renal failure, and hepatic dysfunction. Therefore, the safety threshold of 50 mg/kg/day propylene glycol (equivalent to 0.603 mg/kg/day diazepam) was determined by EMA in patients with impaired liver or renal function.

The decision to use DIAZEM at doses that would exceed the corresponding EMA exposure limit for propylene glycol should be made on a case-by-case basis and after careful consideration of the potential benefits and risks of treatment. If treatment is deemed appropriate, medical monitoring is necessary.

The additive effect of DIAZEM treatment with other products containing propylene glycol and/or any substrate for alcohol dehydrogenase and/or any dietary intake of these excipients should be taken into account.

Ethyl alcohol content

Ethyl alcohol, when administered concomitantly with drugs containing propylene glycol or ethanol (ethyl alcohol), may cause ethanol accumulation and adverse effects, especially in young children with low or underdeveloped metabolic capacity – see section 4.3 and Propylene glycol toxicity, above.

A single 20 mg dose of this drug (two ampoules) administered to a 70 kg adult will result in an ethanol exposure of 4.78 mg/kg, which will result in an increase in blood alcohol concentration (BAC) of approximately 0.83 mg/100 ml.

For comparison, the BAC for an adult drinking a glass of wine or 500 ml of beer is likely to be around 50 mg/100ml.

DIAZEM can also be administered by continuous intravenous infusion. An IV infusion of the maximum recommended dose of 10 mg/kg body weight/24 hours for the treatment of tetanus in an adult patient weighing 70 kg will result in administration of 700 mg (70 ampoules) of this drug in a 24-hour period. This will theoretically result in an exposure of 167 mg/kg of ethanol, which may cause an increase in blood alcohol concentration (BAC) of approximately 28.3 mg/100 ml. The effects of alcohol may be reduced when administered as a slow infusion over a 24-hour period.
The additive effect of treatment with DIAZEM and other ethyl alcohol-containing products and/or any dietary ethanol intake should be taken into account.

Risk from concomitant Opioid use

Concomitant use of diazepam and opioids may cause sedation, respiratory depression, coma, and death. Because of these risks, prescribing sedative medications such as benzodiazepines or related medications such as diazepam concomitantly with opioids should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe diazepam concomitantly with opioids, the lowest effective dose should be used and the duration of treatment should be as short as possible (see general dosage recommendations in section 4.2).

Patients should be monitored closely for signs and symptoms of respiratory depression and sedation. In this context, it is strongly recommended to inform patients and their caregivers (if any) to be aware of these symptoms (see section 4.5).

Concomitant use of alcohol/other CNS depressants
Concomitant use of diazepam with alcohol and/or CNS (central nervous system) depressants should be avoided. Such concomitant use tends to increase the clinical effects of diazepam, possibly including severe sedation, clinically significant respiratory and/or cardiovascular depression (see section 4.5).

Tolerance
Loss of efficacy may occur after repeated use for several weeks. In patients with organic cerebral changes (especially arteriosclerosis) or cardiovascular insufficiency, the limits of tolerance may be very wide (see also section 4.3); care should be taken to adapt the dose to such patients.

Dependence
The risk of dependence (physical or psychological) increases with dose and duration of treatment and is greater in patients with a history of alcohol or drug abuse or in patients with a marked personality disorder. Therefore,

- Regular monitoring of such patients is essential
- Routine reuse should be avoided
- treatment should be discontinued gradually

Abuse of diazepam has been reported.

Withdrawal symptoms
The duration of treatment should be as short as possible (see section 4.2).
If physical dependence has developed, abrupt discontinuation of treatment will result in withdrawal symptoms. These include headache, muscle pain, extreme anxiety, tension, restlessness, confusion and irritability, sleep disturbance, diarrhea and mood swings. In severe cases, the following may occur: Psychotic symptoms including a sense of unreality or separation from the body, derealization, depersonalization, states of confusion, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures. Withdrawal symptoms will be worse in patients with a history of dependence on alcohol or other narcotic drugs, but may occur after abrupt discontinuation of therapy in patients who have received normal therapeutic doses for a short period of time.

Rebound insomnia and anxiety
A transient syndrome in which symptoms that led to treatment with a benzodiazepine reoccur in an enhanced form; it may occur on discontinuation of therapy. It may be accompanied by other reactions such as mood swings, anxiety or sleep disturbances, and restlessness. Since withdrawal phenomena / rebound phenomena are greater after abrupt discontinuation of treatment, it is recommended to reduce the dosage gradually.

In patients with epilepsy or other patients with a history of seizures, abrupt discontinuation of diazepam therapy may result in convulsions or an epileptic state. Convulsions may also occur following abrupt discontinuation in people with alcohol or drug dependence.

Discontinuation should be gradual to minimize the risk of withdrawal symptoms.

<u>Duration of treatment</u>
The duration of treatment should be as short as possible depending on the indication (see

section 4.2). The patient should be evaluated after a period of not more than 4 weeks and regularly thereafter, particularly if the patient is asymptomatic, to assess the need for continued treatment. In general, treatment should not last more than 8-12 weeks, including tapering off the drug. It is not appropriate to extend treatment beyond these periods without re-evaluating the situation.

It may be helpful to inform the patient when starting treatment that the treatment will be of limited duration and to explain exactly how the dosage will be gradually reduced. It is also important for the patient to be aware of the possibility of rebound phenomena, thus minimizing anxiety over such symptoms should they occur when the medicinal product is discontinued. In the case of benzodiazepines with a short duration of action, there are indications that withdrawal phenomena may occur within the dosage range, especially when the dosage is high.

Switching from long-acting benzodiazepines to short-acting benzodiazepines may cause withdrawal symptoms. Therefore, it is important to warn the patients on this matter.

Amnesia
Anterograde amnesia may occur even when benzodiazepines are used in the normal dosage range, but this is particularly evident at higher dose levels. The condition usually occurs within a few hours of taking the product and therefore, to reduce the risk, patients should ensure that they can get 7-8 hours of uninterrupted sleep (see also section 4.8). Amnestic effects may be associated with inappropriate behavior.

Mourning / Loss
Psychological adjustment may be inhibited by benzodiazepines.

Psychiatric and 'paradoxical' reactions
Reactions such as restlessness, agitation, irritability, aggression, excitement, confusion, delusions, anger, nightmares, hallucinations, psychoses, inappropriate behavior, and other adverse behavioral effects may occur.

These reactions are more likely in children and the elderly, and utmost caution should be exercised when prescribing benzodiazepines to patients with personality disorders. If they occur, treatment should be discontinued.

Special Patient Groups
Depressed patients
Diazepam should not be used alone to treat depression or anxiety associated with depression, as it may lead to suicide in these patients.

Patients with a history of alcohol and substance addiction and patients using disulfiram
Diazepam should be used with extreme caution in patients with a history of alcohol or drug dependence (risk of abuse/dependence) – see Propylene glycol toxicity and Ethyl alcohol content. Diazepam should not be used with disulfiram due to its ethyl alcohol content. A reaction may occur up to two weeks after discontinuation of disulfiram (see section 4.5).

Patients with phobias and/or chronic psychosis
Diazepam is not recommended (insufficient evidence for efficacy and safety)

Patients with suicidal potential
People with suicidal potential should not access large amounts of diazepam due to the risk of overdose.

Psychotic illness
Benzodiazepines are not recommended for the primary treatment of psychotic illness.

Additional information on special populations
Pediatric patients
Benzodiazepines should not be administered to children without careful consideration of their necessity; the duration of treatment should be kept to a minimum. Due to the propylene glycol and ethyl alcohol content of DIAZEPAM, treatment with recommended doses of diazepam for pediatric patients may correspond to a propylene glycol dose that may exceed the associated EMA exposure limit. In such a case, the decision to use DIAZEM should be made on a case-by-case basis and after careful consideration of the potential benefits and risks of treatment (see section 4.2 and Propylene glycol toxicity and Ethyl alcohol content, above).

Elderly and weak patients
Elderly and weak patients should be given lower doses (see section 4.2). Due to its myorelaxant effect, there is a risk of falls and consequently hip fractures in the elderly.

Hepatic impairment
Benzodiazepines are not used in the treatment of patients with severe hepatic impairment because they can precipitate encephalopathy. Dose reduction may be required in patients with chronic liver disease. Medical monitoring may be required in patients with impaired hepatic function (see section 4.2 and Propylene glycol toxicity).

Renal impairment
Usual precautions should be taken in treating patients with impaired renal function. In renal impairment, the half-life of diazepam is not altered to any clinically significant extent and dose adjustment is usually not necessary. Medical monitoring may be required in patients with impaired renal function (see section 4.2 and Propylene glycol toxicity, above).

Cardiorespiratory failure
A lower dose is recommended in patients with chronic respiratory failure because of the risk of respiratory depression (see section 4.2).

Diazepam injection should be administered with caution to patients in whom a decrease in blood pressure could lead to cardiovascular or cerebrovascular complications.

- Sodium content:

This medicinal product contains sodium less than 1 mmol (23 mg) in 2ml; i.e. it is considered essentially sodium-free.

- DIAZEM ampoules contain propylene glycol. Therefore, it may cause similar symptoms with alcohol.
- This medicinal product contains ethanol (alcohol) at 10.82% by volume, e.g. up to 170.8 mg per dose, equivalent to 4.32 mL of beer per dose, equivalent to 1.8 mL of wine per dose. It may be harmful to those with alcohol addiction. This should be taken into consideration in

pregnant or breastfeeding women, children and patients in high-risk groups such as liver disease or epilepsy.
• DIAZEM contains 3.7 mg benzoic acid in 2 ml. Therefore, it may increase the risk of jaundice in newborn babies.
• DIAZEM contains 31.4 mg benzyl alcohol in 2 ml. It should not be administered to premature babies and newborns.
It may cause toxic reactions and anaphylactoid reactions in infants and children up to 3 years of age.
• Hydrochloric acid was used to adjust the pH of this product.

4.5. Interactions with other medicinal products and other forms of interaction
Particular attention should be paid to the potential effects of drug interactions with diazepam in the elderly.

Opioids
Concomitant use of sedatives such as benzodiazepines or related drugs such as diazepam with opioids increases the risk of sedation, respiratory depression, coma, and death due to additive CNS depressant effects. The dose and duration of concomitant use should be limited (see section 4.4).

• Substances not recommended for concomitant use

Alcohol
Diazepam should not be used concomitantly with alcohol (CNS inhibition enhanced sedative effects: deterioration of the ability to drive/use machines.

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.

• Conditions you need to take attention:

Pharmacodynamic interactions
If diazepam is used concomitantly with other centrally acting agents (general anesthetics and narcotic analgesics), especially compounds that may increase or potentiate the effect of diazepam, such as neuroleptics, anxiolytics/sedatives, hypnotics, antidepressants, anticonvulsants, sedative antihistamines, antipsychotics, caution should be exercised with regard to the pharmacology of these agents. Such concomitant use may increase sedative effects, cause depression of respiratory and cardiovascular functions. Concomitant use of narcotic analgesics may increase psychological dependence due to increased euphoric effects.

Anti-epileptic drugs
Pharmacokinetic studies on potential interactions between diazepam and antiepileptic drugs have produced conflicting results. Increases and decreases in drug levels, as well as no change, have been reported.

Concomitant use of phenobarbital may cause additive CNS effects. There may be an increased risk of sedation and respiratory depression. Phenobarbital is a known inducer of CYP3A4 and increases the hepatic metabolism of diazepam. The effect of diazepam

decreases.

Particular care should be taken in adjusting the dose in the initial stages of treatment.

Side effects may be more pronounced with hydantoins or barbiturates.

Diazepam has been reported to be displaced from protein binding sites by sodium valproate (increased serum levels: increased risk ofsomnolence).

Narcotic analgesics
Increased euphoria may lead to increased psychological dependence.

Other drugs that increase the sedative effect of diazepam
Cisapride, lofexidine, nabilone, disulfiram and muscle relaxants-baclofen, tizanidine, suxamethonium and tubocurarine.

Compounds affecting hepatic enzyme (especially cytochrome P450)
Inhibitors (e.g. cimetidine: isoniazid: erythromycin: omeprazol: Esomeprazole reduces the clearance and may increase the effects of benzodiazepines.

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 benzodiazepines. The effects of benzodiazepines may be increased and prolonged by concomitant use. The dose of the benzodiazepine may need to be reduced.

Rifamycins (rifamycin)
Rifampicin is a potential inducer of CYP3A4 and significantly increases the hepatic metabolism and clearance of diazepam. In a study in healthy subjects administered 600 mg or 1.2 g of rifampicin daily for 7 days, the clearance of diazepam was increased approximately fourfold. Co-administration with rifampicin results in significantly reduced diazepam concentrations. The effect of diazepam decreases. Concomitant use of rifampicin and diazepam should be avoided.

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

Increased sedative effect with alpha-blockers or moxonidine

Dopaminergics
Possible antagonism of levodopa effect

Antiviral agents (atazanavir, ritonavir, delavirdine, efavirenz, indinavir, nelfinavir, saguinavir)
Antiviral agents may inhibit the CYP3A4 metabolic pathway of diazepam. Increased risk of sedation and respiratory depression. Therefore, concomitant use should be avoided.

Zidovudine

Zidovudine clearance is increased by diazepam.

Oral contraceptives
Inhibits the oxidative metabolism of diazepam. The effect of diazepam is increased.

Concomitant administration of diazepam and combined oral contraceptives is known to cause breakthrough bleeding. The mechanism of this reaction remains unknown. Although breakthrough bleeding was observed, contraceptive failure was not reported.

Theophylline
A proposed mechanism is competitive binding of theophylline to adenosine receptors in the brain. It may interfere with the pharmacodynamic effects of diazepam, such as sedation and reduced psychomotor effects.

Caffeine
Concomitant use may result in decreased sedative and anxiolytic effects of diazepam.

Grapefruit juice
Grapefruit juice inhibits CYP3A4 and may increase diazepam plasma concentrations, prolonging sedation and amnesia. Increases the C_{max} value of diazepam by 1.5-fold and the AUC by 3.2-fold (possible additive effect of diazepam). Although this interaction is not likely to be significant in healthy individuals, it is unclear whether other factors, such as the elderly or liver cirrhosis, increase the risk of side effects with concomitant use.

Antipsychotic
Plasma concentrations of zotepine may be increased. Severe hypotension, collapse, loss of consciousness, respiratory depression, and potentially fatal respiratory arrest have been reported in a few patients receiving benzodiazepines and clozapine. Salivary hypersecretion has also occurred. Caution is advised when initiating clozapine therapy in patients receiving diazepam. The risk of hypotension, bradycardia, and respiratory depression is increased when intramuscular olanzapine is administered concomitantly with parenteral benzodiazepines.

Pharmacokinetic interactions
Diazepam is metabolized primarily to the pharmacologically active metabolites N-desmethyldiazepam, tepezepam and oxazepam. The oxidative metabolism of diazepam is mediated by the CYP3A4 and CYP2C19 isoenzymes. Oxazepam and tepezam are also conjugated with glucuronic acid. CYP3A4 and/or CYP2C19 inhibitors may lead to increased diazepam concentrations, while enzyme-inducing drugs such as rifampicin, hypericum perforatum and some antiepileptics may cause significant decreases in plasma concentrations of diazepam.

Carbamazepine
Carbamazepine is a known inducer of CYP3A4 and increases the hepatic metabolism of diazepam. This may result in up to three-fold plasma clearance and a shorter diazepam half-life. The effect of diazepam decreases.

Phenytoin
Phenytoin is a known inducer of CYP3A4 and increases the hepatic metabolism of diazepam. The effect of diazepam decreases.

The metabolism of phenytoin may be increased, decreased, or remain unchanged by diazepam in an unpredictable manner. Therefore, the serum concentration of phenytoin may decrease or increase. Phenytoin concentrations should be monitored more closely when diazepam is

added or discontinued.

Azoles (fluconazole, itraconazole, ketoconazole, voriconazole)
Increased plasma concentration of benzodiazepines due to inhibition of the metabolic pathway via CYP3A4 and/or CYP2C19.

Fluconazole: Co-administration of 400 mg fluconazole on the first day and 200 mg fluconazole on the second day with diazepam increases the AUC of a single 5 mg oral dose of diazepam by 2.5-fold and prolongs the half-life from 31 to 73 hours.

Voriconazole: A study in healthy subjects demonstrated that voriconazole 400 mg twice daily on the first day and 200 mg twice daily on the second day increased the AUC of a single 5 mg oral dose of diazepam by 2.2-fold and prolonged the half-life from 31 to 61 hours.

The adverse effects and toxicity risk of benzodiazepine have increased. Diazepam dosage should be reduced or concomitant use avoided.

Fluvoxamine
Fluvoxamine inhibits both CYP3A4 and CYP2C19, resulting in inhibition of the oxidative metabolism of diazepam. Co-administration with fluvoxamine, Co-administration with fluvoxamine results in an increase in the half-life of diazepam and an increase in plasma concentrations (AUC) of approximately 190%. Drowsiness, decreased psychomotor performance, and memory impairment may occur. Instead, benzodiazepines that are metabolized by a non-oxidative pathway should preferably be used.

Corticosteroids
Chronic use of corticosteroids may result in increased metabolism of diazepam due to induction of the cytochrome P450 isoenzyme CYP3A4 or the enzymes responsible for glucuronidation. The effects of diazepam are reduced.

Cimetidine
Cimetidine inhibits the hepatic metabolism of diazepam, reducing its clearance and prolonging its half-life. In a study in which cimetidine 300 mg was administered four times daily for 2 weeks, combined plasma levels of diazepam and its active metabolite desmethyldiazepam were found to be increased by 57%, but reaction times and other motor and intellectual tests were unaffected. The effect of diazepam and the risk of drowsiness increase. Diazepam dose reduction may be necessary.

Omeprazol
Omeprazole inhibits the CYP2C19 metabolic pathway of diazepam. Omeprazole prolongs the elimination half-life of diazepam and increases plasma concentrations (AUC) of diazepam by approximately 30-120%. The effect is observed in extensive metabolizers of CYP2C19, but not in poor metabolizers with low diazepam clearance. The dose of diazepam may need to be reduced as the effect of diazepam increases.

Esomeprazole
Esomeprazole inhibits the CYP2C19 metabolic pathway of diazepam. Co-administration with esomeprazole results in a prolongation of the half-life and an increase in plasma concentrations (AUC) of diazepam of approximately 80%. The dose of diazepam may need to

be reduced as the effect of diazepam increases.

Isoniazid
Isoniazid inhibits the CYP2C19 and CYP3A4 metabolic pathways of diazepam. Co-administration with isoniazid 90 mg twice daily for 3 days resulted in a prolongation of the elimination half-life of diazepam and a 35% increase in plasma concentrations (AUC) of diazepam. The effect of diazepam is increased.

Itraconazole
Plasma concentrations of diazepam are increased due to inhibition of the CYP3A4 metabolic pathway. In a study in healthy subjects administered 200 mg itraconazole daily for 4 days, it increased the AUC of a single 5 mg oral dose of diazepam by approximately 15%, but there was no clinically significant interaction as determined in psychomotor performance tests. The effect of diazepam is likely to be increased.

Fluoxetine
Fluoxetine inhibits diazepam metabolism via CYP2C19 and other pathways, resulting in higher plasma concentrations and reduced clearance of diazepam. The effect of diazepam is increased. Close monitoring is required when used in combination.

Disulfiram
Decreased metabolism of diazepam results in increased half-life and increased plasma concentrations of diazepam. The elimination of N-desmethyl metabolites of diazepam is slowed, which may cause pronounced sedative effects. Increased risk of CNS inhibition such as sedation.

Cisapride
It accelerates the absorption of diazepam. It temporarily enhances the sedative effects of orally administered diazepam.

Levodopa
Concomitant use with diazepam has resulted in decreased effects of levodopa in a small number of case reports.

Ketamine
Due to similar oxidative processes, diazepam competitively inhibits ketamine metabolism. When used concomitantly with diazepam as a premedication, the half-life of ketamine increases, resulting in increased efficacy. Sedation increases.

Additional information on special populations:
No interaction studies have been conducted.

Pediatric population:
No interaction studies have been conducted.

4.6. Pregnancy and lactation
General recommendation
Pregnancy category “D”.

Women of childbearing potential/Birth control (Contraception)
Since the risk of congenital malformations increases with use in the first trimester of pregnancy, its use is not recommended in women of childbearing potential and it is recommended to use an appropriate birth control method.

If diazepam is prescribed to a woman of childbearing potential, she should be warned to discontinue diazepam or to seek medical attention if pregnancy is suspected.

Pregnancy
No evidence of safety or harm from animal studies regarding diazepam in human pregnancy.

DIAZEM contains propylene glycol (see sections 2 and 4.4). Although propylene glycol has not been shown to cause reproductive or developmental toxicity in animals or humans, it may reach the fetus. DIAZEM should not be used during pregnancy, especially in the first and last trimesters, unless there is a compelling reason.

If diazepam is prescribed to a woman of childbearing potential, the patient should be advised to contact her physician regarding discontinuation of diazepam if she plans to become pregnant or suspects that she is pregnant.

Results of retrospective studies suggest an increased risk of congenital malformations in mothers and their babies who took diazepam during the first trimester of pregnancy.

Babies born to mothers who take benzodiazepines chronically in the later stages of pregnancy may develop physical dependence and be at risk of developing withdrawal symptoms in the postnatal period.

An increase in fetal heart rate has occurred after the use of diazepam during labor. Hypoactivity, hypotonia, hypothermia, apnea, feeding problems, hyperbilirubinemia, and kernicterus have been reported in neonates born to mothers who received high doses of diazepam (usually greater than 30 mg) shortly before birth.

Breastfeeding
Diazepam has been detected in breast milk. DIAZEM contains propylene glycol, which is also found in breast milk (see sections 2 and 4.4). Administration of DIAZEM to breast-feeding patients should be considered on a case-by-case basis.

Fertility
Animal studies in rats have shown a decrease in pregnancy rate and fewer surviving offspring at high doses. No data are available for human.

4.7. Effects on the ability to drive and use machines
Sedation, amnesia and impairment of muscle function may impair the ability to drive or operate machinery. The likelihood of impaired alertness may increase with inadequate sleep (see also section 4.5). Patients should be warned that even after a single dose, central nervous system effects may persist into the next day.

This medication may impair cognitive functions and affect the patient's ability to drive safely. When prescribing this medication, patients should be told the following:

- The medicine may affect your ability to drive.
- Do not drive without knowing how the medicine affects you.

4.8. Undesirable effects

Drowsiness, apathy, decreased alertness, confusion, fatigue, headache, dizziness, muscle weakness, ataxia, or diplopia occur mainly at the beginning of treatment, but usually disappear with repeated administration. Elderly patients may get confusion at high doses. Elderly patients taking benzodiazepines are at increased risk of falls and associated fractures.

Increased salivation and bronchial secretions have been reported, especially in children.

Amnesia

Anterograde amnesia may occur with therapeutic dosages, with the risk increasing at higher dosages. Amnestic effects may be associated with inappropriate behavior (see section 4.4).

Dependence

Chronic use (even at therapeutic doses) can lead to the development of physical and psychological dependence: Discontinuation of treatment may result in withdrawal or rebound effects (see section 4.4). Abuse of benzodiazepines has been reported.

The incidence of adverse events is listed as follows: 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); not known (cannot be estimated from available data)**.**

Blood and lymphatic system disorders

Rare : Blood dyscrasias
Very rare : Leukopenia, thrombocytopenia, agranulocytosis

Immune system disorders

Very rare : Hypersensitivity reactions including anaphylaxis

Metabolism and nutrition disorders

Unknown : Metabolic disturbances such as metabolic acidosis, increased anion gap, and hyperosmolality have been reported as a consequence of propylene glycol toxicity (see section 4.4 Special warnings and precautions for use).

Psychiatric disorders

Common : Confusion
Rare : Psychiatric and paradoxical reactions such as excitation, restlessness, agitation, irritability, aggression, delusions, anger, hallucinations, psychoses, memory loss, nightmares, inappropriate behavior and other adverse behavioral effects
Apathy, decreased alertness and depression. [b]-

Nervous system disorders

Very common : Somnolence
Common : Ataxia, impaired motor ability, tremors
Uncommon : Anterograde amnesia. [c], Concentration problems, balance disorders, headache, dizziness, speech disorders
Rare : Loss of consciousness, insomnia, slurred speech (dysarthria)

Eye disorders

Unknown : Reversible visual disturbances: Blurred vision diplopia, nystagmus

Ear and labyrinth disorders
Not known : Vertigo

Cardiac disorders
Rare : Bradycardia, heart failure including cardiac arrest

Vascular disorders
Rare : Hypotension, syncope. The incidence of hypotension can be reduced by not exceeding the recommended administration rate. Patients should be kept in the supine position throughout the procedure.
Not known : Intravenous injections of diazepam may be associated with local reactions and thrombophlebitis and venous thrombosis may occur.

Respiratory, thoracic and mediastinal disorders
Uncommon : Respiratory depression
Rare : Respiratory arrest, increased bronchial secretion
Not known : Apnea, worsening of obstructive pulmonary disease

Gastrointestinal disorders
Uncommon : Gastrointestinal disorders (nausea, vomiting, constipation, diarrhea), increased salivation
Rare : Dry mouth, increased appetite

Hepatobiliary disorders
Rare : Jaundice, changes in hepatic parameters (ALT, AST, alkaline phosphatase elevation)

Skin and subcutaneous tissue disorders
Uncommon : Allergic skin reactions (-erythema, skin rashes and itching)

Musculoskeletal, connective tissue and bone disorders
Uncommon : Myasthenia

Renal and urinary tract disorders
Rare : Urinary retention, incontinence

Reproductive system and breast disorders
Rare : Gynecomastia, impotence, increased or decreased libido

General disorders and administration site conditions
Common : Fatigue, withdrawal symptoms (anxiety, panic, palpitations, sweating, tremors, gastrointestinal disorders, irritability, aggression, impaired sensory perception, muscle spasms, general weakness, loss of appetite, paranoid psychosis, delirium, epileptic attacks, headache, muscle pain, depression, insomnia, restlessness, confusion and formation of rebound effect). [d]
Not known : Anaphylaxis, pain or irritation at the injection site (see also Vascular disorders)

Laboratory tests
Very rare : Increased transaminases

[a] Known to occur with use of benzodiazepines or benzodiazepine-like agents. These reactions can be quite severe. It is more likely to occur in children and the elderly. If these symptoms occur, DIAZEM should be discontinued (see section 4.4).
[b] May reveal symptoms of pre-existing depression during benzodiazepine use.
[c] May occur using therapeutic doses, risk increases at higher doses. Amnestic effects may be associated with inappropriate behavior (see section 4.4).
[d] The likelihood and degree of withdrawal symptoms depend on the duration of treatment, degree of dependence, and dose level. In severe cases, the following symptoms may occur: derealization, depersonalization, tinnitus, numbness and tingling of extremities, hypersensitivity to light, noise, and physical contact, involuntary movements, hyperreflexia, tremor, nausea, vomiting, diarrhea, abdominal cramps, loss of appetite, agitation, palpitations, tachycardia, panic attack, vertigo, short-term memory loss, hallucinations/delirium, catatonia, hyperthermia, convulsions. Convulsions may be more common in patients with preexisting seizure disorders or in patients taking other medications that lower the convulsive threshold, such as antidepressants.

Additional information on special populations:
Pediatric and geriatric patients:
Paradoxical reactions (restlessness, agitation, irritability, instability, aggressiveness, anger, obsession, nightmares, psychosis, hallucinations, inappropriate behavior) occurring with benzodiazepines are more likely in children and the elderly.

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 and treatment

Symptoms:
Symptoms of diazepam overdose are mainly intensification of therapeutic effects (ataxia, drowsiness, dysarthria, sedation, muscle weakness, deep sleep, hypotension, bradycardia, nystagmus) or paradoxical excitation. In most cases, only vital functions need to be monitored.

It may lead to coma, areflexia, cardiovascular depression and apnea, requiring appropriate measures against overdose (ventilation, cardiovascular support). Benzodiazepine respiratory depressant effects are more severe in patients with severe chronic obstructive respiratory disease. Severe effects of overdose include rhabdomyolysis and hypothermia.

Rarely, propylene glycol toxicity has been reported at higher than recommended doses (see section 4.4 Special warnings and precautions for use).

Treatment:
Ensure an open airway and adequate ventilation.

In symptomatic patients, level of consciousness, respiratory rate, pulse oximetry, and blood pressure should be monitored. Consider arterial blood gas analysis in patients with decreased level of consciousness (GCS <8; AVPU scale P or U) or decreased oxygen saturation on pulse oximetry.

Correct hypotension by elevating the foot of the bed and giving appropriate fluid. Given that hypotension is primarily due to decreased systemic vascular resistance, drugs with alpha-adrenergic activity such as norepinephrine or high-dose dopamine (10 to 30 mcg/kg/min) may be helpful. Inotrope dosage should be titrated according to blood pressure.

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

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

Benzodiazepines are poorly dialyzed.

Flumazenil, a benzodiazepine antagonist, is not recommended as a routine diagnostic test in patients with reduced consciousness. It can sometimes be used as an alternative to ventilation in children who are sensitive to benzodiazepines or in COPD patients to prevent the need for ventilation. It is not necessary or appropriate in cases of poisoning to completely reverse the effects of benzodiazepines. Flumazenil has a short half-life (about one hour) and an infusion may be required. Flumazenil is contraindicated when patients are taking multiple medications, especially after concomitant use of a benzodiazepine and a tricyclic antidepressant or any seizure-causing drug. This is because a benzodiazepine can suppress seizures caused by the latter drug; antagonism by flumazenil can produce severe status epilepticus that is very difficult to control.

The use of flumazenil is not recommended in epileptic patients receiving long-term benzodiazepine treatment. Although flumazenil has a mild intrinsic anticonvulsant effect, sudden suppression of the protective effect of a benzodiazepine agonist may cause convulsions in epileptic patients.

Contraindications to the use of flumazenil include features suggestive of tricyclic antidepressant use, including a wide QRS or dilated pupil. Its use is also contraindicated in patients with postcardiac arrest.

It should be used with caution in patients with a history of seizures, head trauma, or chronic benzodiazepines.

Occasionally a ventilator may be necessary, but usually few problems are encountered, although behavioural changes are likely in children.

If excitation occurs, barbiturates should not be used.

The effects of overdose with centrally acting drugs, especially when taken with alcohol and in the absence of supportive measures, can be fatal.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Benzodiazepine derivatives.
ATC code: N05BA01

Diazepam is a benzodiazepine tranquilizer with anticonvulsant, sedative, muscle relaxant and amnesic properties. It is used to treat anxiety and tension, as a sedative and prodrug, in the control of muscle spasms as in tetanus, and in the treatment of alcohol withdrawal symptoms. Orthopedic procedures are important in patients undergoing endoscopy and cardioversion.

5.2. Pharmacokinetic properties

General properties

Absorption:
Diazepam is largely (>90%) absorbed following oral administration. When diazepam is administered with a moderately fatty meal, the absorption of diazepam is reduced or delayed.

Distribution:
Diazepam and its metabolites are highly bound to plasma proteins. Additionally, they cross the blood-brain and placental barriers. Diazepam and its metabolites are found in breast milk at concentrations of approximately 1:10 that 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 metabolized into two active metabolites, one of which, desmethyldiazepam, has a prolonged half-life. Diazepam is therefore a long-acting benzodiazepine and repeated doses may lead to accumulation.

Elimination:
Diazepam is metabolized in the liver and excreted via the kidneys. Impaired hepatic or renal function may prolong the duration of action of diazepam. Elderly and weak patients are advised to take half the normal recommended dose initially.

During long-term administration, e.g. in the treatment of tetanus, the dosage should generally be reduced after 6-7 days to reduce the possibility of accumulation and prolonged CNS depression.

Linearity / Non-linearity:
There is no data.

5.3. Preclinical safety data

Diazepam, the active substance of DIAZEM 10 mg/2 ml Solution for IM/IV Injection has been used in Türkiye and various countries in the world for years, and all information about this substance is placed in standard monographs and in the books covering vademecum. Possible adverse effects of its use are available in relevant sections (see 4.4. Special warnings and precautions for use, 4.5. Interactions 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
Hydrochloric acid
Water for injection (q.s.)

6.2. Incompatibilities

DIAZEM should not be mixed with other drugs or IV fluids and should not normally be

diluted except when administered slowly in large volume intravenous infusions with 0.9% sodium chloride solution and 5% dextrose solution.

In compatibility studies conducted with 0.9% sodium chloride solution and 5% dextrose solution, it was shown that the solutions obtained by diluting at a concentration of approximately 0.1 mg/ml were compatible for 24 hours at room conditions.

In cases where administration by IV infusion is deemed necessary, it is recommended to mix "DIAZEM 10 mg/2 ml Solution for IM/IV Injection" with at least 200 ml of 0.9% sodium chloride infusion solution or 5% dextrose infusion solution and use it immediately. Solutions to be administered via IV infusion must be diluted in a glass bottle and applied from there.

6.3. Shelf life
60 months.

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

6.5. Nature and contents of the container
Amber-colored, ringed, Type I glass ampoules of 2 ml each (high-strength borosilicate glass). Each cardboard box contains 10 or 100 ampoules of 2 ml each.

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
DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No:1
34303 Küçükçekmece – İSTANBUL / TÜRKİYE

8. MARKETING AUTHORIZATION NUMBER
113/27

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Date of first authorization : 06.11.1972
Date of renewal of authorization : 03.10.2011

10. DATE OF REVISION OF THE TEXT