

Package leaflet: Information for the user

Diazepam Macure 5 mg/ml, emulsion for injection diazepam

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Diazepam Macure is and what it is used for
2. What you need to know before you are given Diazepam Macure
3. How Diazepam Macure is given
4. Possible side effects
5. How to store Diazepam Macure
6. Contents of the pack and other information

1. What Diazepam Macure is and what it is used for

Diazepam Macure belongs to a group of medicines called benzodiazepines. These have an anxiety-relieving, calming and muscle-relaxing effect.

Diazepam Macure can be used in adults for the treatment of:

- anxiety
- seizures
- alcohol withdrawal symptoms
- premedication before surgical or diagnostic procedures
- anaesthesia initiation and conscious anaesthesia
- spasms related to lockjaw (tetanus)

Diazepam Macure can be used in paediatric patients for the treatment of:

- seizures
- premedication before surgical or diagnostic procedures
- spasms related to lockjaw (tetanus)

2. What you need to know before you are given Diazepam Macure

Do not use Diazepam Macure

- If you are allergic (hypersensitive) to diazepam (or other benzodiazepines), soya, peanut or any of the other ingredients of this medicine (listed in section 6).
- If you have a condition called myasthenia gravis, which causes the muscles to weaken and tire easily.
- If you suffer from sleep apnea (a sleep disorder where you have abnormal pauses in your breathing during sleep).
- If you have severe liver disease.
- If you have acute breathing difficulties (slow and/or shallow breathing).

Warnings and precautions

Talk to your doctor or pharmacist before using Diazepam Macure if you:

- have an alcohol or drug problem, you should tell the doctor before you are given Diazepam Macure.
- are being treated with other medicines that affect the nervous system (e.g. opioids and other benzodiazepines).

- are elderly as Diazepam Macure can cause confusion and affect muscles, which can lead to falls and injuries.
- have breathing problems.
- suffer from depression.
- have suicidal thoughts.
- have epilepsy or a history of seizures.
- have reduced kidney function.

Mental side effects

Contact your doctor if you experience side effects such as agitation, hyperactivity, restlessness, aggressiveness, nightmares or hallucinations. These side effects are more likely to occur in children or the elderly (see section 4).

Amnesia

You may experience memory loss when you receive this medicine. Memory loss is most likely to occur when you receive high doses of Diazepam Macure and can be reduced by getting 7-8 hours of uninterrupted sleep.

Dependence

When taking this medicine there is a risk of dependence, which increases with the dose and duration of treatment and also in patients with a history of alcoholism and drug abuse. Therefore, you should take Diazepam Macure for as short period of time as possible.

Tolerance

If after a few weeks you notice that this medicine is not working as well as it did when first starting treatment, you should speak to your doctor

Withdrawal

Treatment with Diazepam Macure should be gradually withdrawn. Withdrawal symptoms occur with Diazepam Macure even when normal doses are given for short periods of time. See Section 3, 'If you stop taking Diazepam Macure'.

Children and adolescents

Diazepam Macure should only be used in children after careful assessment of the need. The duration of treatment should be kept to a minimum. Safety and effectiveness of diazepam in children below the age of 6 months have not been established.

Other medicines and Diazepam Macure

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Especially:

- antidepressants (e.g. fluvoxamine, fluoxetine)
- antipsychotics (antipsychotics such as clozapine)
- remedies for allergies (antihistamines)
- means for full anaesthesia
- tranquilizers (sedatives)
- sleeping aids (hypnotics)
- muscle relaxants (e.g. suxamethone, tubocurarine)
- some strong painkillers such as morphine (opioids)
- agents for the treatment of epilepsy and mental disorders (barbiturates such as phenobarbital).

If you take these medicines together with Diazepam Macure, the effect of Diazepam Macure can be both strengthened and weakened. Among other things, they can affect your mental state, make you

very sleepy and slow your breathing and lower your blood pressure:

- Disulfiram to treat alcohol dependence.
- Medication against epilepsy such as phenytoin and carbamazepine,
- Opioids for the treatment of pain, cough or as an anaesthetic.
- Theophylline to treat asthma and other breathing problems.
- Cimetidine, omeprazole or esomeprazole medicines that reduce the amount of stomach acid.
- Rifampicin to treat infection (an antibiotic).
- Atazanavir, ritonavir, delavirdine, efavirenz, indinavir, nelfinavir or saquinavir, medicines for viral infections.
- Fluconazole, itraconazole, ketoconazole or voriconazole to treat fungal infection.
- Isoniazid to treat tuberculosis.
- Birth control pills. Breakthrough bleeding can occur when diazepam is taken together with birth control pills, but the preventive effect is not reduced.
- Adrenocortical hormones medicine to treat inflammation in the body.
- Levodopa to treat Parkinson's disease.
- Valproic acid for the treatment of epilepsy and mental disorders.
- Ketamine (an anaesthetic) as diazepam increases the effect of ketamine.
- **Opioids** (eg, strong pain relievers, replacement therapy medications, and some cough medications) can increase the risk of drowsiness, difficulty breathing, or coma, and can be life-threatening. Because of this, concomitant use should only be considered when other treatments are not possible. If your doctor prescribes Diazepam Macure together with opioids, the dose and duration of concomitant treatment should be limited by your doctor. Tell your doctor about all opioid medicines that you take and follow your doctor's recommendations carefully. It may be a good idea to inform friends or family to be aware of the above signs and symptoms. Contact your doctor if you get these symptoms.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine.

Pregnancy

If you are pregnant, you will normally not be treated with Diazepam Macure since there is a low risk of cleft palate in the baby if given during early pregnancy. If this medicine is given during the last 3 months there is a risk that the baby experience side effects such as low body temperature, lethargy or breathing difficulties.

However, as seizures in the mother may also affect the baby negatively, this medicine may be used if your doctor consider the need for treatment larger than the risk of side effects in the baby. If it is used, lowest possible dose will be given, for the shortest period of time.

Breastfeeding

Diazepam is excreted in breast milk, and should therefore not be used during breastfeeding.

Driving and using machines

Diazepam Macure can cause side effects (uncertain movements, tremors, lethargy and fatigue) which can affect occupational safety and the ability to drive safely in traffic. These effects may persist for several days after discontinuing treatment with diazepam. You must not drive a car, motorcycle or bicycle, and you must not work with tools or machines.

Use of Diazepam Macure together with food, drink and alcohol

It is recommended not to drink alcohol while you are using Diazepam Macure. Alcohol may increase the sedative effects of Diazepam Macure and make you very sleepy.

You should not drink grapefruit juice while being treated with Diazepam Macure, as it may affect the effect of the medicine.

Diazepam Macure contains sodium

This medicine contains less than 1 mmol (23 mg) of sodium per ml, that is to say essentially ‘sodium-free’.

Diazepam Macure contains soya oil

If you are allergic to peanut or soya, do not use this medicinal product.

3. How Diazepam Macure is given

The dose of this medicine is individual and will be based on your condition and your age and weight. The dose will be decided by your doctor and will be as low as possible, and used for as short time as possible.

Diazepam Macure may be given as an intramuscular injection or as a slow intravenous injection.

If you are given more Diazepam Macure than you should

As the medicinal product is administered in hospital, overdose is not likely to occur. Signs of an overdose may include loss of muscle coordination, sleep-like drowsiness, confusion, slurred speech, and muscle weakness. An extreme overdose can cause coma (unconsciousness where it is not possible to wake the person), low body temperature (hypothermia), low blood pressure, slow pulse and severe breathing difficulties.

If you stop using Diazepam Macure

Your doctor will decide when you should no longer use this medicine, as he may wish to gradually reduce the number of injections you use before stopping them completely. If treatment with Diazepam Macure is stopped suddenly, you may experience unpleasant side effects, including headaches, muscle pain, anxiety, tension, restlessness, confusion and irritability.

The likelihood and severity of withdrawal symptoms depends on the duration of treatment, the size of the dose and the degree of dependence.

If you have epilepsy or have had seizures and you suddenly stop taking Diazepam Macure, there is a risk of seizures or prolonged epileptic seizures. There is also a risk of seizures if you have an alcohol or drug abuse problem and you suddenly stop receiving Diazepam Macure.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The following side effects have been seen with Diazepam Macure:

Serious side effects

Uncommon (may affect up to 1 in 100 people):

- Very slow and/or shallow breathing (respiratory depression).

Rare (may occur in up to 1 in 1,000 people):

- Respiratory arrest
- Unconsciousness
- Yellowing of the skin and the whites of the eyes
- Cardiac arrest.

Very rare (may affect less than 1 in 10,000 people):

- Severe allergic reaction with symptoms such as sudden wheezing, swelling of the lips, tongue and throat or body, rash, fainting or difficulty swallowing (anaphylaxis).

Other side effects

Very common (may affect more than 1 in 10 people):

- Lethargy.

Common (may affect up to 1 in 10 people):

- Fatigue
- Withdrawal symptoms (for possible symptoms, see point 3)
- Confusion
- Loss of muscle coordination (ataxia) and other movement disorders
- Tremor.

Uncommon (may affect up to 1 in 100 people):

- Muscle weakness
- Memory loss
- Difficulty concentrating
- Balance disorders
- Dizziness
- Headache
- Slurred speech
- Gastrointestinal problems such as nausea, vomiting, constipation, diarrhoea
- Increased saliva secretion
- Allergic skin reactions in the form of itching, skin redness and swelling as well as skin rash.

Rare (may occur in up to 1 in 1,000 people):

- Excitement
- Unrest
- Restlessness
- The feeling of being irritated
- Aggressiveness
- Memory loss
- Delusions
- Tantrums
- Psychoses
- Nightmare
- Inappropriate behavior
- Hallucinations
- Decreased alertness
- Depression
- Emotional numbness
- Sleep problems (insomnia)
- Difficulty speaking
- Slow heart rate (bradycardia)
- Low blood pressure
- Fainting (syncope)
- Increased mucus in the lungs
- Dry mouth
- Increased appetite
- Changes in certain liver enzymes seen in blood tests
- Inability to urinate, loss of bladder control (leakage of urine)
- Enlargement of mammary glands in men
- Impotence, changes in sex drive (libido).

Very rare (may affect less than 1 in 10,000 people):

- Low white blood cell count (leukopenia)
- High concentrations of certain enzymes in the blood (transaminase).

Not known (frequency cannot be determined from the available data):

- Blurred vision, double vision and involuntary eye movements.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via

HPRA Pharmacovigilance

Website: www.hpra.ie

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Diazepam Macure

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the ampoule and the box after 'EXP'. The expiry date refers to the last day of the month.

After first opening the product must be used immediately.

Do not use this medicine if you notice any visible signs of deterioration.

Store below 30 °C.

Do not freeze.

Keep the ampoule in the outer carton in order to protect from light.

Do not throw away medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Content of the pack and other information

What Diazepam Macure contains

- The active substance is diazepam. Each ml of the emulsion for injection contains 5 mg diazepam.
- The other ingredients are soya oil, refined; triglycerides, medium-chain; glycerol; egg phospholipids for injection; sodium oleate; water for injections.

What Diazepam Macure looks like and contents of the pack

The emulsion liquid is a milky white oil-in-water emulsion in a clear glass ampoule.

The cardboard box contains 10 ampoules of 2 ml made of colourless glass.

Marketing Authorisation Holder

Macure Pharma ApS
Hejrevej 39
2400 København NV
Denmark

Manufacturer

B. Braun Melsungen AG
Mistelweg 2
12357 Berlin
Germany

This leaflet was last revised in

The following information is intended for healthcare professionals only:

Instructions for use

If a continuous infusion is required Diazepam Macure can be added to a dextrose solution 5 % or 10 % to achieve a final diazepam concentration within the range 0.08-0.20 mg/ml (i.e. 4-10 ml Diazepam Macure per 250 ml dextrose solution). The minimum infusion rate should be 4 ml/h. A dextrose solution containing added Diazepam Macure should be used within 6 hours of admixture when stored in a glass bottle. Storage in plastic containers is not recommended. Diazepam Macure can be mixed in all proportions with Lipofundin MCT/LCT 10 % or 20 %.

Diazepam Macure should be used by infusion only with the solutions which have been shown to be compatible. As with other diazepam injections, diazepam sorption, including adsorption and absorption to plastic infusion equipment, in particular made of PVC or PU, may occur. This adsorption occurs to a lesser degree with Diazepam Macure than with aqueous diazepam injection preparations when mixed with dextrose solutions.