**Patient leaflet: Information for the user**

**Xilmac® 4 mg/ml solution for injection**

lorazepam

**Read all of this leaflet carefully before you start taking 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, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**



## 1. What Xilmac Injection is and what it is used for

This medicine contains lorazepam, which is a member of a group of medicines called benzodiazepines. It helps to relieve anxiety and muscle tension.

Xilmac Injection is usually prescribed as premedication before surgery or uncomfortable or prolonged investigations. It may also be used to relieve acute anxiety states, acute excitement or acute mania, and in the control of convulsions.

You must talk to a doctor if you do not feel better or if you feel worse.

Xilmac Injection is not recommended for use in children under the age of 12 years except for status epilepticus where Xilmac Injection can be used in adults and children 1 month of age and older.

## 2. What you need to know before you use Xilmac Injection

Tell your doctor or pharmacist if you have been given Xilmac Injection before taking any other medicine, if you become pregnant or if you enter hospital for treatment.

**You should not be given Xilmac Injection:**

- If you have severe breathing or chest problems
- If you have been prescribed benzodiazepines before and found them to be unsuitable
- If you are allergic to benzodiazepines, including lorazepam or any of the other ingredients of this medicine (listed in section 6)
- If you have ‘myasthenia gravis’ (very weak or tired muscles)
- If you have serious liver problems

- If you suffer from ‘sleep apnoea’ (breathing problems when you are asleep)
- If you are an out-patient unless you have somebody to take you home.

**Warnings and precautions**

Talk to your doctor, pharmacist or nurse before using Xilmac Injection:

- If you are pregnant, trying to become pregnant or are breast feeding
- If you are a drug user or heavy drinker
- If you have any kidney or liver problems
- If you are elderly or debilitated (weak)
- If you are suffering or have suffered from depression
- If you have a personality disorder
- If you have a history of psychotic illness
- If you have a history of convulsions/seizures
- If you suffer from breathing problems
- If you suffer from eye problems such as glaucoma
- If you are taking any other medicines, since they may affect the way Xilmac Injection works, Xilmac Injection may also affect the way other drugs work

**Tolerance and dependence**

Tolerance to benzodiazepines may occur. Therefore the beneficial effect of Xilmac may be less apparent after several weeks of use.

Lorazepam may have abuse potential, especially in patients with a history of drug and/or alcohol abuse.

Dependence is unlikely to occur but the risk increases with higher doses and longer-term use and is further increased in patients with a history of alcoholism, drug abuse or in patients with personality disorders. Therefore use in individuals with a history of alcoholism or drug abuse should be avoided.

Dependence may lead to withdrawal symptoms, especially if treatment is discontinued abruptly. Therefore, the drug should always be discontinued gradually – using the oral preparation if necessary.

Some people feel sleepy after receiving Xilmac Injection. Therefore, you may need to stay in hospital for at least 8 hours, or overnight, after receiving your injection. If you are to leave hospital shortly after receiving Xilmac Injection you should have someone with you.

Some elderly patients may feel dizzy after receiving Xilmac Injection and may be in danger of falling.

Transient memory loss has been reported following administration of benzodiazepines.

**Children**
Children can be especially sensitive to the excipients of Xilmac (see “Xilmac Injection contains benzyl alcohol, propylene glycol and polyethylene glycol”).

**Other medicines and Xilmac Injection**

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

In particular, you should tell your doctor if you are taking any other sedative, anti-anxiety drugs, antidepressants, strong pain killers (e.g. opioids, methadone - keep the dosages and duration of both medicines to a minimum as recommended by your doctor), drugs for epilepsy, antihistamines, drugs for

mood or mental disorders (e.g. haloperidol or chlorpromazine). Taking Xilmac with these pain killers may make you more sleepy and in rare cases can cause breathing difficulty and death. Barbiturates (sedatives) and anaesthetics (drugs that cause anaesthesia - reversible loss of sensation), clozapine (drugs for mood or mental disorders), sodium valproate (used in the treatment of epilepsy and bipolar disorder), probenecid (drugs used for gout), theophylline, aminophylline (drugs for respiratory diseases), disulfiram (drug used to support the treatment of chronic alcoholism) and metronidazole (an antibiotic). The dose of these drugs may need to be reduced before you are given Xilmac Injection. You should also tell your doctor if you are taking a drug called scopolamine which may be used for gut problems or before an operation.

Tell your doctor or pharmacist if you have been given Xilmac Injection before taking any other medicine, if you become pregnant or if you enter hospital for treatment.

**Xilmac Injection with food, drink and alcohol**

You should avoid alcohol for at least 24 to 48 hours after receiving Xilmac Injection. Please refer to section 3.

**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 taking this medicine.

Pregnancy
Benzodiazepines, including Xilmac, may cause damage to the foetus if given during early pregnancy. Therefore, if you are pregnant or might become pregnant you should not be given this medicine without consulting your doctor. If you receive this medicine during late pregnancy or during labour, your baby, when born, may be less active than other babies, have a low body temperature, be floppy or have breathing or feeding difficulties for a while. Your baby's response to the cold might be temporarily impaired also. If this medicine is given regularly in late pregnancy, your baby may develop withdrawal symptoms after birth.
Additionally, Xilmac Injection contains benzyl alcohol, a preservative that may cross the placenta.
Xilmac Injection also contains propylene glycol (see "Xilmac Injection contains benzyl alcohol, propylene glycol and polyethylene glycol").

Breast-feeding
Xilmac should not be given to breastfeeding mothers unless the expected benefit to the mother outweighs the potential risk to the infant, as the drug may pass into breast milk.
Additionally, Xilmac Injection contains benzyl alcohol, a preservative that may pass into breast milk.
Xilmac Injection also contains propylene glycol (see "Xilmac Injection contains benzyl alcohol, propylene glycol and polyethylene glycol").

**Driving and using machines**

Some people feel sleepy or dizzy during the day when taking Xilmac. Do not drive or use machinery within 24 to 48 hours of receiving Xilmac Injection.

If you are an out-patient you should not be given Xilmac Injection unless you have somebody to take you home.

**Xilmac Injection contains benzyl alcohol, propylene glycol and polyethylene glycol.**

Xilmac Injection contains 20.9 mg benzyl alcohol in each ampoule equivalent to 20.9 mg/ml.
Xilmac Injection contains 822.6 mg propylene glycol in each ampoule which is equivalent to 822.6 mg/ml.

Xilmac Injection contains 202.5mg polyethylene glycol in each ampoule which is equivalent to 202.5 mg/ml.

Benzyl alcohol may cause allergic reactions. Benzyl alcohol has been linked with the risk of severe side effects including breathing problems (called "gasping syndrome") in young children.

Medicines containing benzyl alcohol should not be given to newborn babies (up to 4 weeks old) and should not be used for more than a week in young children (less than 3 years old), unless advised by the doctor.

Ask your doctor or pharmacist for advice if you are pregnant or breast feeding. This is because large amounts of benzyl alcohol can build-up in your body and may cause side effects (called "metabolic acidosis").
Ask your doctor or pharmacist for advice if you have a liver or kidney disease. This is because large amounts of benzyl alcohol can build-up in your body and may cause side effects (called "metabolic acidosis").

If your child is less than 5 years old, talk to your doctor or pharmacist before giving them this medicine, in particular if they are being given other medicines that contain propylene glycol or alcohol.

If you are pregnant or breast-feeding, do not take this medicine unless recommended by your doctor. Your doctor may carry out extra checks while you are taking this medicine.

If you suffer from a liver or kidney disease, do not take this medicine unless recommended by your doctor. Your doctor may carry out extra checks while you are taking this medicine.

If you are treated with disulfiram (drug used to support the treatment of chronic alcoholism) or metronidazole (an antibiotic), do not take this medicine unless recommended by your doctor.

There have been reports of polyethylene glycol toxicity (e.g. acute tubular necrosis) during administration of Xilmac Injection, including at higher than recommended doses.

## 3. How to take Xilmac Injection

Your doctor will give you Xilmac Injection by injecting it into one of your veins or into one of your muscles.

The recommended dose is:
For pre-medication, you will normally be given 0.05 mg of Xilmac for each kilogram that you weigh (e.g. if you weigh 70 kilograms you will probably receive 3.5 mg of Xilmac). Xilmac Injection is not recommended for the treatment of pre-medication in children under 12 years of age.

For acute anxiety, the usual dose is 0.025 to 0.03 mg for each kilogram that you weigh (e.g. if you weigh 70 kilograms you will probably receive 1.75 to 2.1 mg of Xilmac). Xilmac Injection is not recommended for the treatment of acute anxiety in children under 12 years of age.

Your doctor may prescribe a different dose or length of treatment, especially if you are an elderly or debilitated (weak) patient.

Patients with Renal or Hepatic Impairment: Lower doses may be sufficient in these patients. Use in patients with severe hepatic insufficiency is contraindicated.

When Xilmac Injection is used to control status epilepticus a dose of 4 mg is usually given intravenously to adults. Children receive a lower dose of 0.1 mg per each kilogram of their bodyweight, given

intravenously. Not to exceed 4 mg/dose. If the convulsions persist within the next 10-15 minutes the doctor might decide to give a second dose.

**Dependence on benzodiazepines may occur following prolonged treatment. Therefore Xilmac is usually prescribed for one or two doses, or for a short course of treatment.** This reduces the risk of becoming dependent on Xilmac or suffering unpleasant effects when you stop taking it. (See 'If you stop using Xilmac Injection', below).

You will be prescribed the lowest effective dose for the shortest possible time.

If Xilmac Injection is given at doses that are much higher than those above, unwanted effects such as those shown in "Section 4 Possible side effects" may be more likely. Tell your doctor if you experience any of these effects or any other unwanted effects.

Instructions for use:

Xilmac ampoules are equipped with the OPC (One Point Cut) opening system and must be opened using the following instructions:

- hold with one hand the bottom part of the ampoule
- Put the other hand on the top of the ampoule positioning the thumb above the coloured point and press

**If you stop using Xilmac Injection**

After you have finished your prescribed treatment with Xilmac Injection, your doctor will decide whether or not you need further treatment.

Following a course of treatment, your dose of Xilmac Injection may be reduced slowly. This allows your body to get used to being without Xilmac and reduces the risk of unpleasant effects.

**Withdrawal symptoms**

On stopping Xilmac, you may experience withdrawal symptoms such as headaches, muscle pain, anxiety, tension, depression, restlessness, dizziness, nausea, diarrhoea, loss of appetite, insomnia, confusion, irritability, agitation, shaking, stomach pain, changes in heart rate, short-term memory loss, dysphoria (feelings of sadness (depressed mood), anxiety, irritability, or restlessness), high body temperature and sweating. If these symptoms do occur, they do not usually last for long. If you suffer from any of these symptoms, ask your doctor for advice.

If you suffer from any of the following withdrawal symptoms: loss of the sense of reality, feeling unreal or detached from life and unable to feel emotion, tinnitus (ringing sounds in your ears), numbness or tingling of your arms or legs, vomiting, twitching, hallucinations, convulsions, or effects on sight, hearing or touch, ask your doctor for advice immediately.

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.**

Severe allergic reactions can occur with benzodiazepine use, even after the first dose. Symptoms include swelling of the tongue or throat, shortness of breath, throat closing, nausea or vomiting. In such cases, immediate medical attention should be sought.

Benzodiazepines, including lorazepam, may lead to potentially fatal breathing problems.

Occasionally, you may have unwanted effects whilst taking Xilmac Injection These are usually not serious and do not last long. However, you should tell your doctor if any of the following symptoms are severe or become troublesome:

**Other side effects that may occur are:**
Very common: may affect more than 1 in 10 people

- sedation
- fatigue
- drowsiness

Common: may affect up to 1 in 10 people

- muscle weakness
- asthenia (loss of strength)
- ataxia (poor muscle control)
- confusion
- depression
- unmasking of depression (revealing signs of depression that were previously hidden)
- dizziness

Uncommon: may affect up to 1 in 100 people

- nausea
- change in libido
- impotence
- decreased orgasm

Not known: frequency cannot be estimated from the available data

- increased sensitivity to light, sound and touch
- convulsions/fits
- constipation, yellowing of the skin and eyes
- shaking
- problems with vision (double and blurred vision)
- slurred speech
- headache
- memory loss
- heightened emotions
- coma
- thoughts or attempts of suicide
- impaired attention/concentration
- loss of inhibitions
- increase in specific liver enzymes (bilirubin, liver transaminases and alkaline phosphatase)
- anxiety, excitation, hostility, aggression, sexual arousal
- balance disorder
- difficulty breathing
- difficulty breathing when you are asleep
- worsening of lung disease
- allergic skin reactions (e.g. rash, swelling)
- alopecia (loss of hair from the head or body)
- hypersensitivity reactions
- angioedema (swelling of the face, hands and feet)

- SIADH - syndrome of inappropriate antidiuretic hormone hypersecretion (a condition in which the body produces too much antidiuretic hormone (ADH). Increased ADH may cause too much water to remain inside your body.)
- hyponatremia (low level of sodium in the blood which can cause tiredness and confusion, muscle twitching, fits and coma)
- hypothermia
- lowering of blood pressure
- thrombocytopenia (unexplained bruising, nosebleeds and/or bleeding gums), agranulocytosis (severe infection), pancytopenia (bleeding, bruising easily, fatigue, shortness of breath, and weakness)
- vertigo
- problems sleeping

The following side effects may be more likely to occur in children and elderly patients:
- restlessness
- agitation
- irritability
- aggressiveness
- violent anger
- nightmares
- hallucinations
- personality changes
- abnormal behaviour
- false beliefs

On rare occasions people notice pain, inflammation of the skin or rash at the injection site. Tell your doctor immediately if this happens to you.
If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

**Reporting of side effects**
If you get any side effects, talk to your doctor, pharmacist or nurse. 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 Xilmac Injection

Keep this medicine out of the sight and reach of children. It could harm them.

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

Xilmac Injection should be stored in a refrigerator between 2°C and 8°C and kept in the outer carton to protect from light.

Do not throw away any 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. Contents of the pack and other information

**What Xilmac Injection contains**

The active ingredient in Xilmac Injection is lorazepam and there are 4 mg of lorazepam in each 1 ml of the solution for injection.

Xilmac Injection also contains polyethylene glycol (macrogol 400), benzyl alcohol and propylene glycol (E 1520) (see section 2 “Xilmac Injection contains benzyl alcohol, propylene glycol and polyethylene glycol”).

**What Xilmac Injection looks like and the contents of the pack**

Xilmac Injection is a clear colourless solution supplied in small clear glass bottles (called ampoules) and each ampoule contains 1 ml of Xilmac Injection.
Xilmac Injection is supplied in packs of 10 ampoules.

Do not use if solution has developed a colour or precipitate.

Not all pack sizes may be marketed.

**Marketing Authorisation Holder and Manufacturer**

**Marketing Authorisation Holder**

Macure Healthcare Ltd
62 archlight Building
Triq L-Gharbiel
Is-Swieqi
Malta

**Manufacturer**

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**Company Contact Address:**
info@macurepharma.com

Date leaflet last revised:

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**The following information is intended for healthcare professionals only:**

**Posology and method of administration**

Posology

Dosage and duration of therapy should be individualised. The lowest effective dose should be prescribed for the shortest time possible. The risk of withdrawal and rebound phenomena is greater after abrupt discontinuation; therefore, the drug should be discontinued gradually in all patients.

Method of administration

Xilmac Injection can be given intravenously or intramuscularly. However, the intravenous route is to be preferred. Care should be taken to avoid injection into small veins and intra-arterial injection.

Absorption from the injection site is considerably slower if the intramuscular route is used and as rapid an effect may be obtained by oral administration of Lorazepam tablets.

Xilmac should not be used for long-term chronic treatment.

**Preparation of the injection**

Intramuscular administration:

A 1:1 dilution of Xilmac Injection with normal saline or Sterile Water for Injection BP is recommended in order to facilitate intramuscular administration.

Intravenous administration:

For intravenous administration, Xilmac Injection should always be diluted with saline or Sterile Water for Injection BP as a 1:1 dilution.

Xilmac Injection is presented as a 1 ml solution in a 2 ml ampoule to facilitate dilution.

Xilmac Injection should not be mixed with other drugs in the same syringe.

**Dosage:**

**Premedication:**
*Adults:* 0.05 mg/kg (3.5 mg for an average 70 kg man). By the intravenous route the injection should be given 30-45 minutes before surgery when sedation will be evident after 5-10 minutes and maximal loss of recall will occur after 30-45 minutes.

By the intramuscular route the injection should be given 1-1$^{1}/_{2}$ hours before surgery when sedation will be evident after 30-45 minutes and maximal loss of recall will occur after 60-90 minutes.

*Paediatric population:* Xilmac Injection is not recommended in children under 12 years.

**Acute Anxiety:**
*Adults:* 0.025-0.03 mg/kg (1.75-2.1 mg for an average 70 kg man). Repeat 6 hourly.

*Paediatric population:* Xilmac Injection is not recommended in children under 12 years.

**Status epilepticus:**
*Adults*: 4 mg intravenously.

*Paediatric population (1 month of age and older)*: 0.1 mg/kg bodyweight intravenously. Maximum 4 mg/dose.

If seizures persist within the next 10-15 minutes, the same dose may be injected again but no more than 2 doses should be given. Not to exceed 4 mg/dose.

*Elderly and debilitated patients:* Elderly and debilitated patients may respond to lower doses and half the normal adult dose may be sufficient.

**Patients with Renal or Hepatic Impairment:**
Lower doses may be sufficient in patients with impaired renal function or with mild to moderate hepatic insufficiency. Use in patients with severe hepatic insufficiency is contraindicated.

**Incompatibilities**

In the absence of compatibility studies this medicinal product must not be mixed with other medicinal products other than those mentioned in "Posology and method of administration".

**Shelf life**

Unopened: 15 months.
After opening: Use immediately after opening.
After dilution: Use immediately after dilution.

**Special precautions for storage**

Store in a refrigerator between 2ºC and 8ºC.

Keep in the outer carton to protect from light.

**Special precautions for disposal and other handling**

Xilmac Injection should not be mixed with other drugs in the same syringe. Do not use if solution has developed a colour or precipitate (see "Posology and method of administration").

No special requirements for disposal.

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