

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Lorazepam Macure 4 mg/ml solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule contains 4 mg/ml lorazepam (4 mg per 1 ml ampoule).

Excipients with known effect: benzyl alcohol, propylene glycol.

Each ml contains 21 mg benzyl alcohol.

Each ml contains 840 mg propylene glycol.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Solution for injection

A clear, colourless or almost colourless hypertonic solution, free from visible particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Lorazepam Macure is indicated in adults and adolescents above 12 years of age:

- As premedication, before surgical procedures or prior to diagnostic procedures.
- For symptomatic treatment of pathological anxiety and tension in patients who, for some reason, are unable to take oral medication.

4.2 Posology and method of administration

Posology

Premedication

For a maximum beneficial effect, the dose should be calculated based on body weight (the usual dose is 2-4 mg) and administered as follows:

a) I.V. administration:

For an optimal effect, doses of 0.044 mg / kg to a maximum of 2 mg should be used, 15-20 minutes before the procedure.

This dose (I.V. administered) will be adequate for sedation of most adult patients and should not normally be exceeded in patients over 50 years of age.

Higher doses, up to 0.05 mg / kg with a maximum of 4 mg, can be administered.

The necessary airway equipment must be available immediately prior to the intravenous administration of Lorazepam Macure.

b) I.M. administration:

The optimal effect is reached by administering 0.05mg/kg to a maximum 4mg, with minimum 2 hours before the forecasted procedure. The dose is individually adjusted.

In elderly or debilitated patients or in patients with impaired renal or hepatic function or with severe respiratory or cardiovascular disease, a dose reduction is recommended.

In case of local anesthesia and in diagnostic procedures requiring patient involvement, the simultaneous use of an analgesic may be appropriate.

The dose should be reduced in case of concomitant administration of central nervous system depressants.

Lorazepam Macure should not be mixed with other drugs in the same syringe.

Symptomatic treatment of pathological anxiety and tension in patients who, for some reason, are unable to take oral medication.

The recommended initial dose is 2-4 mg I.V. or 0.05 mg / kg I.M. (intravenous administration is preferred).

If necessary, the dose may be repeated after 2 hours. As soon as the acute symptomatology is controlled, the patient must receive appropriate treatment for the underlying condition.

The use of lorazepam tablets may be considered if further treatment with benzodiazepines is required.

Pediatric population

The use of Lorazepam Macure in children under 12 years is contraindicated (see section 4.3).

Use in elderly and debilitated patients

Clinical studies have shown that patients over 50 years of age have a deeper and prolonged sedation when lorazepam is administered intravenously.

In normal conditions, a starting dose of 2 mg should be sufficient unless a greater degree of sedation and / or preoperative impairment of memory is desired.

For elderly and debilitated patients reduce the initial dose by approximately 50% and adjust the dosage as needed and tolerated (see section 4.4).

Patients with renal or hepatic insufficiency

Lorazepam Macure is not recommended for use in patients with severe hepatic insufficiency. When Lorazepam Macure is used in patients with mild to moderate hepatic or renal insufficiency, a starting dose of 0.05 mg / kg (but not more than 2 mg) is recommended.

Method of administration

For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Lorazepam Macure should not be administered intra-arterially. As with other injectable benzodiazepines, an intra-arterial injection may cause arterial spasm that causes gangrene and may require amputation.

Lorazepam Macure is also contraindicated in patients with:

- sleep apnoea syndrome;
- severe respiratory insufficiency;
- known hypersensitivity to benzodiazepines;
- myasthenia gravis;
- severe hepatic insufficiency.

Lorazepam Macure is contraindicated in children under 12 years of age.

4.4 Special warnings and precautions for use

Intravenous use

For intravenous use, lorazepam should be diluted with an equal amount of a compatible diluent (see section 6.6).

Intravenous administration should be performed slowly and repeatedly.

One should ensure that the injection does not occur intra-arterially and no perivascular extravasation occurs.

Alcohol

Tolerance for alcohol and other CNS depressants will be diminished in the presence of lorazepam, therefore patients should be advised to either avoid Lorazepam Macure or use a reduced dose.

Alcoholic beverages should not be used for at least 24 to 48 hours after receiving Lorazepam Macure, due to the general additive depressant effect of benzodiazepines on central nervous system.

Reduction of responsiveness / performance

It is recommended that patients treated with lorazepam, remain under observation for 24 hours after administration of the last dose.

If lorazepam is used for short-term procedures on an outpatient basis, the patient must be accompanied by a responsible adult at the time of discharge.

Patients should be warned not to drive vehicles or take activities requiring attention for 24-48 hours after administration. A reduction in performance may persist for extended periods due to patient's high age, concomitant use of other drugs, stress due to surgery, or the general condition of the patient. Patients should also be warned that premature walking (within 8 hours after lorazepam administration) may lead to injury due to traps.

Endoscopic procedures

There are insufficient data to warrant the use of lorazepam in endoscopic procedures in ambulatory patients.

If these procedures are performed in hospitalized patients, adequate observation in a recovery room is necessary and the pharyngeal reflex activity must be reduced by local anesthesia, prior to the endoscopic procedure.

Coma / shock

There are no data that can justify the use of lorazepam in coma or shock.

Concomitant use with scopolamine

Concomitant use of scopolamine is not recommended because this combination may lead to an increased incidence of sedation, hallucinations and irrational behavior.

Risk from concomitant use of opioids

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

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers (where applicable) to be aware of these symptoms (see section 4.5).

Status epilepticus

Caution is required when administering lorazepam to patients with status epilepticus, especially patients who have received other central nervous system depressants or patients who are severely ill.

The possibility of respiratory depression or partial respiratory tract obstruction should be considered. Adequate resuscitation equipment must be available.

Psychotic or depressive disorders

Lorazepam is not intended for primary treatment of psychotic illness or depressive disorders, and should not be used as a monotherapy in depressed patients.

Benzodiazepines may have a disinhibiting effect and may release suicidal tendencies in depressed patients.

Long-term use of lorazepam

There are no data to support a long term use of lorazepam.

Some patients have developed blood dyscrasia during the treatment with benzodiazepines; in some, an increase in the hepatic enzyme values was observed.

If prolonged treatment is considered clinically necessary, regular blood and hepatic function tests are recommended.

Prolonged treatment with benzodiazepines should be gradually reduced.

Elderly patients

As with any premedication, extreme caution is required when administering lorazepam in elderly or severely ill patients and patients with limited lung retention (COPD, sleep apnoea syndrome), due to the possibility of apnea and / or hypoxic heart failure. Resuscitation equipment for ventilation assistance must be readily available.

Lorazepam should be used with caution in elderly due to the risk of sedation and/or musculoskeletal weakness that can increase the risk of falls, with serious consequences in this population. Elderly patients should be given a reduced dose (see section 4.2).

Impaired renal or hepatic function

Patients with impaired renal or hepatic function should be closely monitored and the dosage should be carefully adjusted according to their reactions. Lower doses may be sufficient in these patients.

The same precautions apply to elderly or debilitated patients and patients with chronic respiratory insufficiency.

Renal insufficiency

Lorazepam is not recommended for use in patients with renal insufficiency. If lorazepam is used in patients with mild to moderate hepatic or renal disease, the lowest effective dose should be used as the duration of the effect may be prolonged in those circumstances.

Acute narrow angle glaucoma

Caution is required in the treatment of patients with acute narrow- angle glaucoma.

Paradoxical reactions

Anxiety can be a symptom of various other conditions. It should be taken into account that the patient complaint may be related to an underlying physical or psychiatric condition for which more specific treatment is available.

During treatment with benzodiazepines, paradoxical reactions such as restlessness, agitation, irritability, aggressiveness, despair, anger attacks, nightmares, hallucinations, psychoses and inappropriate behavior were occasionally reported. Such reactions are more likely to occur in children and in the elderly. Should these occur, use of the drug should be discontinued.

Hypotension

Although hypotension has occurred only rarely, benzodiazepines should be administered with caution to patients in whom a drop in blood pressure might lead to cardiovascular or cerebrovascular complications. This is particularly important in elderly patients.

Proximal gastrointestinal disorder

In rats treated with lorazepam for more than one year at a dose of 6 mg / kg / day, an esophagus dilatation was observed. The dose without effect was 1.25 mg / kg / day (approximately 6 times the maximum therapeutic dose in humans, which is 10 mg / day). The effect was only reversible if treatment was discontinued within two months after this phenomenon was first observed. The clinical significance of this is not clear. However, with long-term use of lorazepam and in geriatric patients, caution is necessary and frequent control of symptoms of a proximal gastrointestinal disorder is required. The use of lorazepam for prolonged periods is not recommended.

Anterograde amnesia

Benzodiazepines can cause anterograde amnesia. This usually occurs several hours after ingestion. Therefore, in order to reduce the risk, patients should be able to sleep continuously for 7/8 hours (see also section 4.8).

Paediatric population

The use of lorazepam is contraindicated in children under 12 years (see section 4.3).

After administration of lorazepam especially in neonates with very low birth weight, epileptic seizures and myoclonus were reported.

Drug abuse and dependence

There are no clinical data with regard to abuse or dependence. However, based upon experience with oral benzodiazepines, physicians should be aware that repeated administration of lorazepam over a long period of time may lead to physical and / or psychological dependence.

The risk increases with higher doses and longer-term use and is further increased in patients with a history of alcoholism or drug abuse.

In case of physical dependence, abrupt discontinuation of treatment may be associated with withdrawal symptoms. Symptoms reported following discontinuation of oral benzodiazepines include headaches, muscle pain, anxiety, tension, depression, insomnia, restlessness, confusion, irritability, sweating and rebound symptoms in which the symptoms that gave rise to benzodiazepine treatment increased return. It may be difficult to distinguish these symptoms from the original symptoms for which the product was prescribed.

In severe cases, the following symptoms may occur: derealisation, depersonalisation, hyperacusis, tinnitus, numbness and tingling of the extremities, sensitivity to light, noise and physical contact, involuntary movements, vomiting, hallucinations and convulsions. Convulsions may occur more frequently in patients with pre-existing convulsive disease or in patients using other drugs that reduce the convulsion threshold, such as antidepressants.

Withdrawal symptoms, and especially the more severe ones, occur more frequently in patients treated with high doses over a long period of time. However, withdrawal symptoms are also reported after discontinuation of treatment with benzodiazepines

in therapeutic doses, especially if the treatment is abruptly discontinued. Since the risk of withdrawal symptoms / rebound phenomena is greater if the treatment is abruptly stopped, it should be gradually decreased.

Benzyl alcohol

This medicine contains 21 mg benzyl alcohol in each 1 ml of solution for injection.

Benzyl alcohol may cause allergic reactions.

High volumes should be used with caution and only if necessary, especially pregnant or breast-feeding women or in subjects with liver or kidney impairment because of the risk of accumulation and toxicity (metabolic acidosis).

Propylene glycol

This medicine contains 840 mg propylene glycol in each 1 ml of solution for injection.

4.5 Interaction with other medicinal products and other forms of interaction

Benzodiazepines, including lorazepam, produce additive CNS depressant effects when co-administered with other agents such as alcohol, barbiturates, antipsychotics, sedatives / hypnotics, anxiolytics, antidepressants, narcotic analgesics, sedative antihistamines, anticonvulsants and anesthetics.

Alcohol

Concomitant use with alcohol is not recommended.

Haloperidol

Cases of apnea, coma, bradycardia, cardiac arrest and death have been reported with concomitant use of lorazepam and haloperidol.

Scopolamine

Concomitant use of scopolamine showed an increased incidence of sedation, hallucinations and irrational behavior.

Clozapine

Concomitant use of clozapine and lorazepam may cause marked sedation, excessive salivation and ataxia.

Valproate

Valproate may inhibit the glucuronidation of lorazepam (increased serum levels: increased risk of drowsiness).

Probenecid

Probenecid increases the half-life of lorazepam and reduces the clearance due to inhibition of glucuronidation.

Opioids

The concomitant use of sedative medicines such as benzodiazepines or related drugs such as lorazepam with opioids increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dosage and duration of concomitant use should be limited (see section 4.4).

No interactions with laboratory tests were observed or reported.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are insufficient data on the use of lorazepam during pregnancy. When lorazepam is administered during pregnancy, hypothermia, respiratory depression and hypotonia (Floppy Infant Syndrome) may occur as a result of the pharmacological action of lorazepam in the newborn child.

In case of prolonged use, withdrawal symptoms may occur in the child.

Animal experimental studies do not indicate direct or indirect harmful effects for pregnancy, embryo-developmental development, labor or postnatal development.

Lorazepam Macure should only be used during pregnancy if strictly necessary for a period as short as possible and at the lowest possible dose.

Breastfeeding

Lorazepam passes in small amounts into breast milk. During Lorazepam Macure use, breastfeeding is not recommended.

Fertility

There are no data on possible effects of parenterally administered lorazepam on female fertility.

4.7 Effects on ability to drive and use machines

Like all patients who use central nervous system inhibitors, patients who use lorazepam should be warned that they should not operate dangerous machines or drive vehicles until they are not sleepy or dizzy.

Patients should be advised not to drive vehicles or take activities requiring attention during 24 to 48 hours after lorazepam administration. A reduction of performance may persist for prolonged periods due to the patient's high age, concomitant use of other agents, stress due to surgery or the general condition of the patient.

4.8 Undesirable effects

Side effects are usually observed at the beginning of treatment. They generally become less severe or disappear with continuation of treatment or reduction of the dose.

The reported incidents depend on the dose, route of administration and concomitant use of other drugs that suppress the central nervous system.

The following side effects have been observed with the following frequencies: Very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), not known (cannot be estimated from the available data). Within each frequency group, adverse reactions are ranked by decreasing seriousness.

<i>System Organ Class</i>	<i>Very Common ($\geq 1/10$)</i>	<i>Common ($\geq 1/100$ to $< 1/10$)</i>	<i>Uncommon ($\geq 1/1,000$ to $< 1/100$)</i>	<i>Rare ($\geq 1/10,000$ to $< 1/1,000$)</i>
<i>Blood and lymphatic system disorders</i>				Blood dyscrasia
<i>Psychiatric disorders</i>			Confusion, depression, emotional flattening, sleep disorders, change in libido;	Temporary anterograde amnesia or memory disorder, paradoxical reactions.*
<i>Nervous system disorders</i>		Sedation, drowsiness, dizziness, ataxia	Headache, decreased alertness.	
<i>Eye disorders</i>			Visual disturbances, diplopia.	
<i>Vascular disorders</i>				Hypotension, hypertension.
<i>Gastrointestinal disorders</i>			Nausea, gastrointestinal symptoms.	
<i>Hepatobiliary disorders</i>				Abnormal liver function tests
<i>Skin and subcutaneous tissue disorders</i>			Allergic skin reactions.	
<i>Musculoskeletal and connective tissue disorders</i>		Muscle weakness		
<i>General disorders and administration site conditions</i>	Fatigue			

*During treatment with benzodiazepines, paradoxical reactions such as agitation, nervousness, irritability, aggressiveness, despair, anger attacks, nightmares, hallucinations, psychosis and inappropriate behaviour have been occasionally reported. Such reactions are more likely to occur in children and in the elderly.

After intramuscular administration: pain, burning sensation and redness at the site of injection were reported.

Following intravenous administration: local phlebitis, pain immediately after the injection and redness observed during a 24-hour observation period.

1.6% of patients reported pain immediately after injection, while 0.5% of patients reported pain 24 hours after injection. An intra-arterial injection may lead to arterial spasm, possibly resulting in gangrene for which amputation may be necessary (see section 4.3).

A certain loss of efficacy of the sedative and hypnotic effect of benzodiazepines may occur after repeated use for several weeks.

Tolerance for the effects of benzodiazepines may occur after repeated use.

Pre-existing depression can be manifested when using benzodiazepines.

In patients with severe sedation, partial respiratory tract obstruction may occur. Intravenous administration of lorazepam, alone and in a higher dose than recommended or in the recommended dose together with other agents used during anesthesia, may cause severe sedation.

Therefore, the necessary equipment for keeping the airways open and supporting the respiration / ventilation must be available and should be used if necessary.

Anterograde amnesia may occur with the use of therapeutic doses of lorazepam, the risk increasing at higher doses. Amnestic effects may be accompanied by inappropriate behavior (see also section 4.4).

During lorazepam administration, propylene glycol toxicity (e.g., lactate acidosis, hyperosmolality, hypotension) has been rarely reported.

Other symptoms of propylene glycol toxicity are non-responsiveness, tachypnoea, tachycardia, diaphoresis and central nervous system toxicity, including epileptic seizures and intraventricular haemorrhage. Such symptoms may be expected in patients with renal insufficiency and in children (see also section 4.4).

Drug abuse and dependence (see section 4.4)

The use of lorazepam, (also in therapeutic doses) may lead to physical dependence. Symptoms reported after discontinuation of benzodiazepine treatment include: headache, muscle pain, anxiety, tension, depression, insomnia, restlessness, confusion, irritability, sweating and rebound symptoms, with the symptoms leading to the treatment with benzodiazepines to a greater extent recurrence. It may be difficult to distinguish these symptoms from the original symptoms for which the product was indicated.

In severe cases, the following symptoms may occur: derealization, depersonalization, hyperacusis, tinnitus, numbness and tingling of the extremities, sensitivity to light, sound and physical contact, involuntary movements, vomiting, hallucinations and convulsions.

Convulsions/seizures may be more common in patients with pre-existing seizure disorders or who are taking other drugs that lower the convulsive threshold such as antidepressants.

Convulsions may occur more frequently in patients with a history of convulsions or in patients using other drugs that reduce the convulsion threshold, such as antidepressants.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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

HPRA Pharmacovigilance

Website: www.hpra.ie

4.9 Overdose

Symptoms and treatment of overdose

As with other benzodiazepines, an overdose will not cause a life-threatening situation, except in combination with other drugs with inhibitory effects on the central nervous system (including alcohol).

In the treatment of overdose with any drug, one should keep in mind that the patient may have taken different medicines.

Particular attention should be paid to respiratory and cardiovascular functions on the intensive care.

Overdose with benzodiazepines usually results in different degrees of central nervous system dampening, ranging from sleepiness to coma. In mild cases, symptoms include sleepiness, mental confusion and lethargy. In severe cases, symptoms may occur such as ataxia, hypotension, hypotonia, respiratory depression, rarely coma (stages 1 to 3) and, very rarely, the patient's death.

Flumazenil may be useful as antidote.

Cases of lactic acidosis, hyperosmolality, hypotension possibly related to propylene glycol (excipient) were reported on administration of injectable lorazepam in higher than the recommended doses. The risk of these symptoms is greater in patients with renal insufficiency and in children (see section 4.4).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: benzodiazepine derivatives, ATC code: N05BA06.

Lorazepam is a benzodiazepine. It has anxiolytic, sedative, hypnotic, anticonvulsant and muscle relaxant properties. The exact mechanism of action of benzodiazepines has not yet been fully elucidated. They appear to exert their activity through different mechanisms. Benzodiazepines are likely to exert their effects by binding to specific receptors at different central nervous system sites. Acting like this, they enhance synaptic or presynaptic inhibition achieved by gamma aminobutyric acid, or directly influence the mechanisms responsible for triggering action potentials.

5.2 Pharmacokinetic properties

Absorption

Lorazepam is rapidly absorbed after intramuscular administration. Peak plasma concentrations are reached approximately 60 to 90 minutes after intramuscular administration. The mean elimination half-life of unconjugated lorazepam in human plasma is approximately 12 to 16 hours after intramuscular or intravenous administration. Based on elimination half-life, steady-state concentrations are reached within 3 to 5 days.

Distribution

The volume of distribution volume is 1.11 l / kg. At clinically relevant concentrations, lorazepam is bound to plasma proteins for approximately 90%.

Biotransformation

Lorazepam is metabolized mainly by glucuronic acid conjugation, thereby forming the inactive glucuronide. Lorazepam has no active metabolites.

Seventy to seventy-five percent of the dose is excreted in the urine as glucuronide. Lorazepam is not significantly hydroxylated and is also no substrate for the N-desalkylating enzymes of the cytochrome P450 system.

Elimination

Age has no clinically significant effect on lorazepam kinetics. In one study, a statistically significant decrease in overall clearance was reported in elderly patients, but the elimination half-life was not significantly affected.

In patients with mild to moderate hepatic impairment (hepatitis, cirrhosis due to excessive alcohol consumption) no change in lorazepam clearance was observed.

Renal insufficiency

In single dose pharmacokinetic studies in patients with different degrees of renal insufficiency, ranging from mild to full failure, no significant changes in lorazepam absorption, clearance or excretion were observed. The elimination of the inactive glucuronide metabolite was significantly reduced. In a study in which lorazepam was administered sub-chronically to 2 patients with chronic renal insufficiency, a reduction in elimination and a concomitant prolongation of the elimination half-life of lorazepam was reported. Hemodialysis had no significant effect on the pharmacokinetics of unmetabolized lorazepam but did cause substantial clearance of the inactive plasma glucuronide.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Macrogol
Benzyl alcohol
Propylene glycol

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products other than those mentioned in section 6.6.

6.3 Shelf life

Unopened: 18 months.

Stability after dilution:

Chemical and physical in-use stability has been demonstrated for 1 hour at 2-8°C. From a microbiological point of view, unless the method of opening/dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store and transport refrigerated (2°C – 8°C). Keep in the outer carton to protect from light.
For storage conditions after dilution/first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Lorazepam Macure is packed in Type I (Ph.Eur), clear glass ampoule of 2 ml filling capacity. The ampoules are placed in moulded polyvinyl chloride trays, which are then sealed by a protective PE transparent foil.
The polyvinyl chloride trays are inserted in a carton box together with a leaflet.
Box of 5 and 10 ampoules of 1 ml solution.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Lorazepam Macure is slightly viscous when cool.

Intramuscular administration:

In order to facilitate intramuscular administration, dilution with an equal volume of a compatible solution is recommended, such as 0.9% NaCl, 5% Glucose, Bacteriostatic Water for injection with Benzyl alcohol, Bacteriostatic NaCl for injection- with Benzyl alcohol, Bacteriostatic Water for injection with paraben and Water for injection.
Lorazepam Macure can be also administered undiluted, if given deeply in a large muscle mass.

Intravenous administration:

In case of intravenous administration, Lorazepam Macure should always be diluted with an equal volume of one of the following diluents: 0.9% NaCl, 5% Glucose, Bacteriostatic Water for injection with Benzyl alcohol, Bacteriostatic NaCl for injection with Benzyl alcohol, Bacteriostatic Water for injection with paraben and Water for injection.
The injection rate should not exceed 2 mg / min. Parenteral medicines must be inspected visually for the presence of particles or discolourations prior to administration.

Instructions for dilution for intravenous use

Extract the desired amount of Lorazepam Macure into the syringe, then slowly suck the desired volume of diluent. Retract the piston slightly to provide an additional mixing space. Immediately mix the contents by repeatedly twisting the syringe until a homogeneous solution has formed. Do not shake vigorously as this will cause air bubbles.

Lorazepam Macure should not be mixed with other drugs in the same syringe. Do not use if solution has developed a colour or a precipitate (see section 4.2).

No special requirements for disposal.

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

7 MARKETING AUTHORISATION HOLDER

Macure Pharma ApS
Hejrevej 39
Copenhagen Nv
Hovedstaden
2400
Denmark

8 MARKETING AUTHORISATION NUMBER

PA23199/002/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26th November 2021

Date of last renewal: 23rd May 2024

10 DATE OF REVISION OF THE TEXT

October 2023