Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Lorazepam Macure 4 mg/ml solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml solution contains 4 mg lorazepam. Each ampoule with 1 ml contains 4 mg lorazepam.

Excipients with known effect
Each ml contains 21 mg benzyl alcohol, 840 mg propylene glycol and 189 mg polyethylene 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 a 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. Lorazepam Macure is indicated in adults, adolescents, children and infants from 1 month of age:
- For the control of status epilepticus.

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 administration of 0.05 mg/kg to a maximum of 4 mg, with minimum 2 hours before the forecasted procedure. The dose is individually adjusted.
In patients with severe respiratory or cardiovascular disease, a dose reduction is recommended.

In case of local anaesthesia and in diagnostic procedures requiring patient involvement, 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 I.M. i.e. 0.05 mg/kg (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.

Status epilepticus
Adults: 4 mg intravenously.
Elderly: Elderly may respond to a reduced dose. Half the normal adult dose may be sufficient.

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

The infusion rate must not exceed 2 mg/min.

If the seizure lasts longer than 10-15 minutes, the doctor may decide to administer another dose. A maximum of 2 doses may be administered.
Due to the potential risk of toxicity from accumulation of excipients the maximum dose of Lorazepam Macure should not be repeated within 24 hours in children under 5 years old (see warning regarding excipients in section 4.4).

Paediatric population
The use of Lorazepam Macure in children under 12 years is contraindicated, except for the indication status epilepticus where it is contraindicated in neonates (see section 4.1, 4.3 and 4.4).

Use in elderly and debilitated patients
For elderly and debilitated patients the initial dose must be reduced by approximately 50% and the dosage adjusted as needed and tolerated (see section 4.4).
Clinical studies have shown that patients over 50 years of age have a deeper and prolonged sedation when lorazepam is administered intravenously.

Patients with renal or hepatic insufficiency
Lorazepam Macure is contraindicated for use in patients with severe hepatic insufficiency. When Lorazepam Macure is used in patients with renal or mild to moderate hepatic 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.

Treatment should be in a setting where cardiorespiratory monitoring is possible and resuscitation equipment is available. This is of special importance in infants and elderly patients. See section 4.4.

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, except for the indication status epilepticus where it is contraindicated in neonates.

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 hospitalised patients, adequate observation in a recovery room is necessary and the pharyngeal reflex activity must be reduced by local anaesthesia, 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 behaviour.

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 dyscrasias 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.

Tolerance
Tolerance for the effects of benzodiazepines may occur after repeated use (see section 4.8).

Impaired renal or hepatic function
Lorazepam is not recommended for use in patients with renal and/or hepatic insufficiency.
If lorazepam is used in patients with renal or mild to moderate hepatic insufficiency, the lowest effective dose should be used as the duration of the effect may be prolonged in those circumstances.
Patients with impaired renal or hepatic function should be closely monitored.

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

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 behaviour 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 oesophagus 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 to 8 hours (see also section 4.8).

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).

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, illicit substance 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.

Anaphylactic/anaphylactoid reactions
Severe anaphylactic/anaphylactoid reactions have been reported with benzodiazepine use. Following the first dose or subsequent doses of benzodiazepines, cases of angioedema involving the tongue, glottis or larynx have been reported. Some patients have experienced other symptoms while taking benzodiazepines, such as dyspnoea, swelling of the throat or nausea and vomiting (see section 4.8). Some patients had to be treated as a medical emergency. If angioedema occurs with involvement of the tongue, glottis or larynx, airway occlusion may occur and may be fatal. In patients experiencing angioedema during treatment with a benzodiazepine, re-exposure to the medicinal product should not take place.

Elderly patients
As with any premedication, extreme caution is required when administering lorazepam in elderly or severely ill patients and patients with a limited pulmonary reserve (COPD, sleep apnoea syndrome), due to the possibility of apnoea 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).

Paediatric population
The use of lorazepam is contraindicated in children under 12 years of age, except for the indication status epilepticus where it is contraindicated in neonates (see section 4.1, 4.3 and 4.4).

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

Lorazepam Macure contains benzyl alcohol, polyethylene glycol and propylene glycol (see section 4.4 "Information on excipients"). Children may be hypersensitive to benzyl alcohol, polyethylene glycol and propylene glycol.

Information on excipients
Lorazepam Macure contains benzyl alcohol, polyethylene glycol and propylene glycol.

Risk of excipient accumulation and toxicity in paediatric patients less than 5 years of age and other special populations.

All these excipients are substrates of alcohol dehydrogenase and may saturate metabolism and increase the risk of excipient accumulation that can lead to toxicity. Paediatric patients less than 5 years of age are particularly vulnerable due to immature renal and metabolic capacity.

The risk also includes patients with impaired hepatic or renal function, pregnant or breast-feeding women (see section 4.6), as well as patients with an impaired alcohol and aldehyde dehydrogenase enzyme system.

It is important to take into account the combined daily metabolic burden of co-administration with other substrates of alcohol dehydrogenase (e.g. ethanol). Particular caution should be taken when repeated doses are given.

Further risks for each individual excipient are outlined below.

Propylene glycol
This medicine contains 840 mg propylene glycol in each ampoule, which is equivalent to 840 mg/ml.

Medical monitoring, including measurements of osmolar and/or anion gap, is required in patients with impaired renal or hepatic functions receiving ≥ 50 mg/kg/day propylene glycol. Several adverse reactions attributable to propylene glycol have been reported such as renal dysfunction (acute tubular necrosis), acute renal failure and liver dysfunction.

The population predisposed to propylene glycol accumulation and associated potential adverse events include patients being treated with disulfiram or metronidazole.

Doses of propylene glycol 1 mg/kg/day may cause serious adverse reactions in neonates; doses of ≥ 50 mg/kg/day may cause side effects in children under 5 years of age, especially if the baby or child is receiving other medicinal products containing propylene glycol or alcohol.
Administration of ≥ 50 mg/kg/day propylene glycol to pregnant or breast-feeding women should only be considered on an individual basis (see section 4.6).

Benzyl alcohol
This medicine contains 21 mg benzyl alcohol in each ampoule, which is equivalent to 21 mg/ml.
The preservative benzyl alcohol may cause allergic reactions. Intravenous administration of benzyl alcohol has been associated with serious adverse events and deaths in neonates ("gasping syndrome"). Premature and low birth weight neonates are more likely to develop toxicity. Medicinal products containing benzyl alcohol should not be used for more than 1 week in children under 3 years of age, unless necessary. Although normal therapeutic doses of this product usually release amounts of benzyl alcohol significantly lower than doses reported in association with gasping syndrome, the minimum concentration of benzyl alcohol at which toxicity may occur is unknown.

Polyethylene glycol
Lorazepam Macure contains polyethylene glycol (see section 2). There have been reports of polyethylene glycol toxicity (e.g. acute tubular necrosis) during administration of Lorazepam Macure, including doses higher than recommended.

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 anaesthetics.

Compounds which inhibit certain hepatic enzymes (particularly cytochrome P450) may enhance the activity of benzodiazepines. To a lesser degree this also applies to benzodiazepines which are metabolised only by conjugation.

Alcohol
Concomitant use with alcohol is not recommended.

Haloperidol
Cases of apnoea, 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 behaviour.

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).

Theophylline/aminophylline:
The use of theophylline or aminophylline can reduce the sedative effect of benzodiazepines, including lorazepam.

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.
Animal experimental studies do not indicate direct or indirect harmful effects for pregnancy, embryo-developmental development, labour 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.
If, for compelling medical reasons, the medicinal product is administered during the late phase of pregnancy, or during labour at high doses, effects on the newborn infant such as hypothermia, hypotonia and moderate respiratory depression, apnoea, feeding difficulties and impaired metabolic response to cold stress ("floppy infant syndrome") can be expected due to the pharmacological action of the compound.
Moreover, infants born to mothers who took benzodiazepines chronically during the later stages of pregnancy may have developed physical dependence and may be at some risk for developing withdrawal symptoms in the postnatal period.

Lorazepam Macure contains benzyl alcohol and propylene glycol (see section 4.4). Benzyl alcohol can cross the placenta. Administration of ≥ 50 mg/kg/day propylene glycol to pregnant women should only be considered on an individual basis.

Breastfeeding
As lorazepam is excreted in human milk, it should not be taken during breastfeeding, unless the expected benefit for the woman outweighs the potential risk to the infant.
Lorazepam Macure contains benzyl alcohol and propylene glycol (see section 4.4 "Information on excipients"). Benzyl alcohol present in maternal serum is likely to pass into breast milk.
Propylene glycol has not been shown to cause reproductive or developmental toxicity in animals or humans, but propylene glycol passes into breast milk. Administration of ≥ 50 mg/kg/day of propylene glycol to breast-feeding women should be considered on an individual basis.

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

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 do activities requiring attention in 24 to 48 hours after lorazepam administration. A reduction of performance may persist for prolonged periods depending on the age of the patient, 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 (≥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 the available data). Within each frequency group, adverse reactions are ranked by decreasing seriousness.

System Organ Class	*Very Common*	*Common*	*Uncommon*	*Rare*	Not known
Blood and lymphatic system disorders				Blood dyscrasias.	Thrombocytopenia, agranulocytosis, pancytopenia.
Immune system disorders					Anaphylactic/anaphylactoid reactions, angioedema.
Endocrine disorders					Syndrome of Inappropriate Antidiuretic HormoneHypersecretion (SIADH).
Metabolism and nutrition					Hyponatraemia.

disorders					
Psychiatric disorders		Occurrence of depression.	Confusion, depression, emotional flattening,sleep disorders, change in libido.	Temporary anterograde amnesia or memorydisorder, paradoxical reactions*.	Euphoria, suicidal thoughts/attempts.
Nervous system disorders		Sedation, drowsiness, dizziness, ataxia	Headache, decreased alertness.		Extrapyramidal symptoms, tremor, dysarthria,convulsions/ seizures, coma.
Eye disorders			Visual disturbances, diplopia.		
Vascular disorders				Hypotension, hypertension.	
Respiratory, thoracic and mediastinal disorders					Respiratory depression (dose-dependent inseverity), apnoea, aggravation of sleep apnoea, aggravation of obstructivepulmonary disease.
Gastrointestinal disorders		Vomiting	Nausea, gastrointestinal symptoms.		Constipation.
Hepatobiliary disorders				Abnormal liver function tests	Elevated bilirubin, elevated livertransaminases, elevated alkaline phosphatase.
Skin and subcutaneous tissue disorders			Allergic skin reactions.		Alopecia.
Musculoskeletal and connective tissue disorders		Muscle weakness			
Reproductive system and breast disorders			Change in libido, impotence, decreased orgasm.		
General disorders and administration site conditions	Fatigue				Hypothermia.

*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 doses than recommended or in the recommended dose together with other agents used during anaesthesia, 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 behaviour (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: derealisation, depersonalisation, hyperacusis, tinnitus, numbness and tingling of the extremities, sensitivity to light, sound and physical contact, involuntary movements, vomiting, hallucinations and convulsions.
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.

Lorazepam Macure contains the excipients propylene glycol and polyethylene glycol. Various adverse events have been reported with high doses (500 mg/kg/day or more) or prolonged use of propylene glycol, such as hyperosmolality, lactic acidosis; renal dysfunction (acute tubular necrosis), acute renal failure; cardiotoxicity (arrhythmia, hypotension); central nervous system disorders (depression, coma, seizures); respiratory depression, dyspnoea; liver dysfunction; haemolytic reaction (intravascular haemolysis) and haemoglobinuria; or multisystem organ failure. Such exposure can be achieved if the dose of the product significantly exceeds the recommended dose, see section 2 for content.

Adverse events are usually reversed following weaning off propylene glycol, and in more severe cases following haemodialysis.

Medical monitoring is required.

There have also been reports of toxicity (e.g., acute tubular necrosis) with high doses of polyethylene glycol.

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) Injection is readily and about completely absorbed when given intramuscularly. Peak plasma concentrations occur approximately 60-90 minutes following intramuscular administration.

Distribution
Following intravenous administration, the mean volume of distribution is approximately 1.3 l/kg. Unbound lorazepam penetrates the blood/brain barrier freely by passive diffusion. Lorazepam is approximately 92% bound to human plasma proteins at a lorazepam concentration of 160 ng/ml.

Biotransformation
Lorazepam is metabolised by a simple one-step process to a pharmacologically inactive glucuronide. There is a minimal risk of accumulation after repeated doses, giving a wide margin of safety. The total clearance of lorazepam following intravenous dose is about 1.0-1.2 mg/min/kg.

There are no major active metabolites.
Based on *in vitro* studies, multiple UGT enzymes contribute to the hepatic glucuronidation of R- and S-lorazepam. Both R- and S-lorazepam were glucuronidated by UGT2B4, 2B7 and 2B15; additional hepatic and extrahepatic UGT enzymes also metabolised both R- and S-lorazepam *in vitro*.

Elimination
The elimination half-life is about 12-16 hours when given intramuscularly or intravenously. Following a single 2 mg and 4 mg intravenous dose of lorazepam to small groups of healthy subjects (n=6 and n=7 subjects, respectively), cumulative urinary excretion of lorazepam glucuronide was estimated to be greater than 80% of the dose.

Special populations

Paediatric population
Neonates (birth to 1 month of age): Following a single 0.05 mg/kg (n=4) or 0.1 mg/kg (n=6) intravenous dose of lorazepam, mean total clearance normalised to body-weight, was reduced by 80% compared to normal adults, terminal half-life prolonged 3-fold, and volume of distribution was decreased by 40% in neonates with asphyxia neonatorum compared to normal adults. All neonates were of ≥ 37 weeks of gestational age.

There was no significant age-related difference in body weight normalised clearance in children, adolescents and adults, observed in 50 children aged 2.3-17.8 years. Population pharmacokinetic analysis for paediatric patients (except neonates) also suggested similar pharmacokinetics to adults.

Elderly
Following single intravenous doses of lorazepam 1.5 to 3 mg of lorazepam per injection, mean total body clearance of lorazepam decreased by approximately 20% in elderly subjects compared to younger adults.

Gender
Gender has no effect on the pharmacokinetics of lorazepam.

Renal insufficiency
Single dose pharmacokinetic studies in patients with degrees of renal insufficiency ranging from mild impairment to renal failure, have reported no significant changes in absorption, clearance or excretion of lorazepam. Haemodialysis did not have any significant effect on the pharmacokinetics of intact lorazepam but substantially removed the inactive glucuronide from plasma.

Hepatic insufficiency
No change in the clearance of lorazepam was reported in patients with mild to moderate hepatic impairment (i.e. hepatitis, alcoholic cirrhosis).

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Propylene glycol (E1520)
Polyethylene glycol 400 (macrogol 400)
Benzyl alcohol.

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^{0}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 in order 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 sodium chloride 9 mg/ml (0.9%) solution for injection, glucose 50 mg/ml (5%) 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: sodium chloride 9 mg/ml (0.9%) solution for injection, glucose 50 mg/ml (5%) 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. Do not use if solution has developed a colour or a precipitate.

Instructions for dilution for intravenous use
Extract the desired amount of Lorazepam Macure into the syringe, then slowly extract 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

April 2026