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:
Each ampoule with 1 ml solution contains 21 mg benzyl alcohol, 840 mg propylene glycol and 189 mg/ml macrogol (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

As pre-operative medication or premedication for uncomfortable or prolonged investigations, e.g. bronchoscopy, arteriography, endoscopy.
For the treatment of acute anxiety states, acute excitement or acute mania.
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
Dosage and duration of therapy should be individualised. The lowest effective dose should be prescribed for the shortest time possible.

Prior to starting treatment with Lorazepam, a discussion should be held with patients to put in place a strategy for ending treatment with Lorazepam in order to minimise the risk of dependence, addiction and drug withdrawal syndrome (see section 4.4).

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 1-1½ 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: Lorazepam Macure 4 mg/ml solution for injection is not recommended in children under 12.

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: Lorazepam Macure 4 mg/ml solution for injection is not recommended in children under 12.

Status epilepticus
Adults: 4 mg intravenously.

Paediatric population: 2 mg intravenously.

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 sections 4.1, 4.3 and 4.4).

Elderly: The elderly may respond to lower doses and half the normal adult dose may be sufficient.

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 of age (see section 4.4).

Patients with renal or hepatic impairment
Lower doses may be sufficient in these patients (See section 4.4). Use in patients with severe hepatic insufficiency is contraindicated.

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

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

Lorazepam Macure 4 mg/ml solution for 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.

Lorazepam Macure should not be used for long-term chronic treatment.

4.3 Contraindications

Hypersensitivity to the active substance, benzodiazepines or to any of the excipients listed in section 6.1.
Acute pulmonary insufficiency.
Sleep apnoea syndrome.
Myasthenia gravis.
Severe hepatic insufficiency.

Lorazepam Macure 4 mg/ml solution for injection is not recommended for out-patient use unless the patient is accompanied.

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

Prior to use
Lorazepam Macure 4 mg/ml solution for injection may be diluted for IM administration and should always be diluted for IV administration with equal amounts of compatible diluent (see section 4.2).
Intravenous injection should be administered slowly except in the control of status epilepticus where rapid injection is required.

After use
It is recommended that patients receiving lorazepam should remain under observation for at least eight hours and preferably overnight. When lorazepam is used for short procedures on an outpatient basis, the patient should be accompanied when discharged.

Respiratory distress
The possibility that respiratory arrest may occur or that the patient may have partial airway obstruction should be considered. Therefore, equipment necessary to maintain a patent airway and to support respiration/ventilation should be available and used where necessary.

Use of benzodiazepines, including lorazepam, may lead to potentially fatal respiratory depression. Extreme care must be taken in administering lorazepam to elderly or very ill patients and to those with limited pulmonary reserve or compromised respiratory function (e.g. chronic obstructive pulmonary disease [COPD]), because of the possibility that apnoea and/or cardiac arrest may occur. Care should also be exercised when administering lorazepam to a patient with status epilepticus, especially when the patient has received other central nervous system depressants.

Severe anaphylactic/anaphylactoid reactions have been reported with the use of benzodiazepines.

Cases of angioedema involving the tongue, glottis or larynx have been reported in patients after taking the first or subsequent doses of benzodiazepines. Some patients taking benzodiazepines have had additional symptoms such as dyspnoea, throat closing, or nausea and vomiting. Some patients have required medical therapy in the emergency department. If angioedema involves the tongue, glottis or larynx, airway obstruction may occur and be fatal. Patients who develop angioedema after treatment with a benzodiazepine should not be rechallenged with the drug.

Drug dependence, tolerance and potential for abuse

Drug addiction comprises behavioural, cognitive and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use and possible tolerance or physical dependence. Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, which manifests as withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug. Addiction and dependence are related but distinct presentations and in discussing these themes, terminology that apportion blame to the individual should be avoided.
For all patients, prolonged use of this product may lead to drug dependence and addiction but can occur with short-term use at recommended therapeutic doses. The risks are increased in individuals with current or past history of substance misuse disorder (including alcohol misuse) or mental health disorder (e.g., major depression).
Additional support and monitoring may be necessary when prescribing for patients at risk of drug misuse.
A comprehensive patient history should be taken to document concomitant medications, including over-the-counter medicines and medicines obtained on-line, and past and present medical and psychiatric conditions.
Patients may find that treatment is less effective with chronic use and express a need to increase the dose to obtain the same level of symptom control as initially experienced. Patients may also supplement their treatment with additional medications to achieve the same effect. These could be signs that the patient is developing tolerance. The risks of developing tolerance should be explained to the patient.
Overuse or misuse may result in overdose and/or death. It is important that patients only use medicines that are prescribed for them at the dose they have been prescribed and do not give this medicine to anyone else.
Patients should be closely monitored for signs of misuse, abuse, or addiction.
The clinical need for treatment with Lorazepam should be reviewed regularly, with frequent assessments of patients being undertaken during the course of their treatment.
Drug withdrawal syndrome
Prior to starting treatment with Lorazepam, a discussion should be held with patients to explain the risk of dependence, addiction, and drug withdrawal syndrome. A withdrawal strategy for ending treatment with Lorazepam should also be put in place with the patient before starting treatment (there may be exceptions to this in specific clinical situations such as symptom management in end of life palliative care).
Drug withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. When a patient no longer requires therapy, it is advisable to taper the dose gradually to minimise symptoms of withdrawal. Tapering from a high dose may take in excess of weeks or months. Patients should be informed of this when the medication is first prescribed.
The reduction schedule for a patient should be tailored to the individual and should be modified to allow intolerable withdrawal symptoms to improve before making the next reduction. If using a published withdrawal schedule, apply it flexibly to accommodate the person’s preferences, changes to their circumstances and the response to dose reductions.

Suggest a slow stepwise rate of reduction proportionate to the existing dose, so that decrements become smaller as the dose is lowered, unless clinical risk is such that rapid withdrawal is needed.

Psychiatric illness
Lorazepam is not intended for the primary treatment of psychotic illness or depressive disorders, and should not be used alone to treat depressed patients. The use of benzodiazepines may have a disinhibiting effect and may release suicidal tendencies in depressed patients.

Pre-existing depression may emerge during benzodiazepine use.

Anxiety or insomnia may be a symptom of several other disorders. The possibility should be considered that the complaint may be related to an underlying physical or psychiatric disorder for which there is more specific treatment.

Alcohol
Patients should be advised that their tolerance for alcohol and other CNS depressants will be diminished in the presence of lorazepam. Alcoholic beverages should not be consumed for at least 24 to 48 hours after receiving lorazepam.

Risk from concomitant use of opioids
Concomitant use of benzodiazepines 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).

Coma/shock
There is no evidence to support the use of lorazepam in coma or shock.

Narrow-angle glaucoma
Caution should be used in the treatment of patients with acute narrow-angle glaucoma.

Renal or hepatic impaired function
As with all benzodiazepines, the use of lorazepam may worsen hepatic encephalopathy.
As with all CNS-depressants, the use of benzodiazepines may precipitate encephalopathy in patients with severe hepatic insufficiency. Therefore, use in these patients is contraindicated.

Patients with impaired renal or hepatic function should be monitored frequently and have their dosage adjusted carefully according to patient response. Lower doses may be sufficient in these patients. The same precautions apply to elderly or debilitated patients and patients with chronic respiratory insufficiency.

Blood tests
Some patients taking benzodiazepines have developed a blood dyscrasia, and some have had elevations in liver enzymes. Periodic haematologic and liver-function assessments are recommended where repeated courses of treatment are considered clinically necessary.

Anterograde amnesia
Transient anterograde amnesia or memory impairment has been reported in association with the use of benzodiazepines. This effect may be advantageous when lorazepam is used as a premedicant.

Paradoxical reactions
Paradoxical reactions have been occasionally reported during benzodiazepine use (see section 4.8). Such reactions may be more likely to occur in children and 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.

Elderly patients
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
Lorazepam Macure contains benzyl alcohol, propylene glycol and macrogol (see section 4.4).

Excipient information

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.

Benzyl alcohol
Lorazepam Macure contains 21 mg benzyl alcohol in each ampoule, which is equivalent to 21 mg/ml (see section 2). The preservative benzyl alcohol may cause hypersensitivity reactions. Intravenous administration of benzyl alcohol has been associated with serious adverse events, and death in paediatric patients including 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 ordinarily deliver

amounts of benzyl alcohol that are substantially lower than those reported in association with the “gasping syndrome”, the minimum amount of benzyl alcohol at which toxicity may occur is not known.

Propylene glycol
Lorazepam Macure contains 840 mg propylene glycol in each ampoule, which is equivalent to 840 mg/ml (see section 2). Medical monitoring, including measurement of the osmolar and/or anion gap, is required in
patients with impaired renal and/or hepatic function who receive ≥50 mg/kg/day of propylene glycol. Various adverse effects attributed to propylene glycol have been reported, such as renal dysfunction (acute tubular necrosis), acute renal failure and liver dysfunction.

The population with a predisposition for accumulation of propylene glycol and the associated potential adverse effects include patients treated with disulfiram or metronidazole.

Propylene glycol doses of ≥1 mg/kg/day may induce serious adverse effects in neonates, while doses of ≥50 mg/kg/day may induce adverse effects in children less than 5 years old, in particular if the baby or the child is given other medicines that contain propylene glycol or alcohol.

Administration of ≥50 mg/kg/day of propylene glycol to pregnant or lactating women should only be considered on a case by case basis (see section 4.6).

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

4.5 Interaction with other medicinal products and other forms of interaction

Alcohol

Concomitant intake with alcohol is not recommended.

The sedative effects may be enhanced when the product is used in combination with alcohol. This affects the ability to drive or use machines.

Benzodiazepines, including lorazepam, produce additive CNS depressant effects including respiratory depression, when co-administered with other medications which themselves produce CNS depression, e.g. opioids, barbiturates, antipsychotics, sedatives/hypnotics, anxiolytics, antidepressants, narcotic analgesics, sedative antihistamines, anticonvulsants and anaesthetics (see section 4.4).

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).

Valproate

Concurrent administration of lorazepam with sodium valproate may result in reduced clearance (20 to 40%) and increased concentrations of lorazepam. Therefore clinical monitoring is advised and lorazepam dosage should be reduced when appropriate.

Probenecid

Concurrent administration of lorazepam with probenecid may result in reduced clearance, increased elimination half-life and increased concentrations of lorazepam. Therefore clinical monitoring is advised and lorazepam dosage should be reduced when appropriate.

Narcotic analgesics

An enhancement of the euphoria induced by narcotic analgesics may occur with benzodiazepine use, leading to an increase in psychic dependence.

Cytochrome P450 inhibitor

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.

Scopolamine

The addition of scopolamine to lorazepam is not recommended, since their combination has been observed to cause an increased incidence of sedation, hallucination and irrational behaviour.

Clozapine

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

Theophylline or aminophylline

Administration of theophylline or aminophylline may reduce the sedative effects of benzodiazepines, including lorazepam.

Haloperidol

There have been reports of apnoea, coma, bradycardia, heart arrest and death with the concomitant use of lorazepam injection solution and haloperidol.

4.6. Fertility, pregnancy and lactation

Pregnancy

Lorazepam should not be used during pregnancy, especially during the first and last trimesters, unless in the judgement of the physician such administration is clinically justifiable. Benzodiazepines may cause foetal damage when administered to pregnant women.

If the drug is prescribed to a woman of childbearing potential, she should be warned to contact her physician about stopping the drug if she intends to become, or suspects that she is, pregnant.

Use of lorazepam during the late phase of pregnancy may require ventilation of the infant at birth.

If, for compelling medical reasons, the product is administered during the late phase of pregnancy, or during labour at high doses, effects on the neonate, such as hypothermia, hypotonia and moderate respiratory depression, can be expected, due to the pharmacological action of the compound.

Infants of mothers who ingested benzodiazepines for several weeks or more preceding delivery have been reported to have withdrawal symptoms during the postnatal period.

Symptoms such as hypotonia, hypothermia, respiratory depression, apnoea, feeding problems, and impaired metabolic response to cold stress have been reported in neonates born of mothers who have received benzodiazepines during the late phase of pregnancy or at delivery.

There are insufficient data regarding obstetrical safety of parenteral lorazepam, including use in caesarean section. Such use, therefore, is not recommended.

Lorazepam Macure contains benzyl alcohol and propylene glycol (see section 4.4 'Excipient Information'). Benzyl alcohol can cross the placenta. Propylene glycol has not been shown to cause reproductive or developmental toxicity in animals or humans, however, it may reach the foetus. Administration of ≥50 mg/kg/day propylene glycol to pregnant women should only be considered on a case by case basis.

Breast-feeding
Since benzodiazepines are found in breast milk, lorazepam should not be given to breast-feeding mothers unless the expected benefit to the woman outweighs the potential risk to the infant.

Lorazepam Macure contains benzyl alcohol and propylene glycol (see section 4.4 'Excipient Information'). Benzyl alcohol present in maternal serum is likely to cross into human milk and may be orally absorbed by a nursing infant. Propylene glycol has not been shown to cause reproductive or developmental toxicity in animals or humans, however, it has been found in milk and may be orally absorbed by a nursing infant. Administration of ≥50 mg/kg/day propylene glycol to lactating women should only be considered on a case by case basis.

4.7 Effects on ability to drive and use machines

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988.

When prescribing this medicine, patients should be told:

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you
- It is an offence to drive while under the influence of this medicine
- However, you would not be committing an offence (called 'statutory defence') if:
  - The medicine has been prescribed to treat a medical or dental problem and
  - You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
  - It was not affecting your ability to drive safely

Sedation, amnesia, impaired concentration and impaired muscular function may adversely affect the ability to drive or use machines. Therefore, patients should not drive or operate machinery within 24-48 hours of administration of lorazepam and should be advised not to take alcohol (see section 4.5).

4.8 Undesirable effects

System Organ Class	*Very Common (≥ 1/10)*	*Common (≥1/100 to <1/10)*	*Uncommon (≥1/1,000 to <1/100)*	*Frequency not known (cannot be estimated from the available data)*
Blood and lymphatic system disorders				Thrombocytopenia, agranulocytosis, pancytopenia
Immune system disorders				Hypersensitivity reactions, anaphylactic/oid reactions
Endocrine disorders				SIADH
Metabolism and nutrition disorders				Hyponatremia
Psychiatric disorders	Drug dependence (see section 4.4)	Confusion depression, unmasking of depression	Change in libido, decreased orgasm	Disinhibition, euphoria, suicidal ideation/attempt, paradoxical reactions, including anxiety, agitation, excitation, hostility, aggression, rage, sleep disturbances/insomnia, sexual

System Organ Class	*Very Common (≥ 1/10)*	*Common (≥1/100 to <1/10)*	*Uncommon (≥1/1,000 to <1/100)*	*Frequency not known (cannot be estimated from the available data)*
				arousal, hallucinations
Nervous system disorders±	Sedation, drowsiness	Ataxia, dizziness		Extrapyramidal symptoms, tremor, dysarthria/ slurred speech, headache, convulsions/ seizures, amnesia, coma, impaired attention/ concentration, balance disorder
Eye disorders				Visual disturbances (including diplopia and blurred vision)
Ear and labyrinth disorders				Vertigo
Vascular disorders				Hypotension, lowering in blood pressure
Respiratory, thoracic and mediastinal disorders				Respiratory depression$^{\beta}$, apnea, worsening of sleep apnea, worsening of obstructive pulmonary disease
Gastrointestinal disorders			Nausea	Constipation
Hepatobiliary disorders				Jaundice
Skin and subcutaneous tissue disorders				Angioedema, allergic skin reactions, alopecia
Musculoskeletal and connective tissue disorders		Muscle weakness		
Reproductive system and breast disorders			Impotence	
General disorders and administration	Fatigue Drug	Asthenia		Hypothermia

System Organ Class	*Very Common (≥ 1/10)*	*Common (≥1/100 to <1/10)*	*Uncommon (≥1/1,000 to <1/100)*	*Frequency not known (cannot be estimated from the available data)*
site conditions	withdrawal symptoms (see 4.4 Special warnings and precautions).			
Investigations				Increase in bilirubin, increase in liver transaminases, increase in alkaline phosphatase

± Benzodiazepine effects on the CNS are dose-dependent, with more severe CNS depression occurring with high doses.

Symptoms reported following discontinuation of benzodiazepines include headaches, muscle pain, anxiety, tension, depression, insomnia, restlessness, confusion, irritability, sweating, and the occurrence of "rebound" phenomena whereby the symptoms that led to treatment with benzodiazepines recur in an enhanced form. These symptoms may be difficult to distinguish from the original symptoms for which the drug was prescribed.

In severe cases the following symptoms may occur: derealisation; depersonalisation; hyperacusis; tinnitus; numbness and tingling of the extremities; hypersensitivity to light, noise, and physical contact; involuntary movements; hyperreflexia, tremor, nausea, vomiting; diarrhoea, abdominal cramps, loss of appetite, agitation, palpitations, tachycardia, panic attacks, vertigo, short-term memory loss, hallucinations/delirium; catatonia; hyperthermia, convulsions. Convulsions 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.

β The extent of respiratory depression with benzodiazepines is dose-dependent, with more severe depression occurring with high doses.

Tolerance at the injection site is generally good although, rarely, pain and redness have been reported after lorazepam.

Transient anterograde amnesia or memory impairment may occur using therapeutic doses, the risk increasing at higher doses (see section 4.4).

Paediatric population

Paradoxical reactions may be more likely to occur in children and the elderly (see section 4.4).

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 the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Patients should be informed of the signs and symptoms of overdose and to ensure that family and friends are also aware of these signs and to seek immediate medical help if they occur.

Symptoms
In the management of overdosage with any drug, it should be borne in mind that multiple agents may have been taken.

Overdosage of benzodiazepines is usually manifested by degrees of central nervous system depression ranging from drowsiness to coma. In mild cases, symptoms include drowsiness, mental confusion and lethargy. In more serious cases, and especially when other CNS-depressant drugs or alcohol are ingested, symptoms may include ataxia, hypotension, hypotonia, respiratory depression, cardiovascular depression, coma and, very rarely, death.

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

These adverse events usually reverse following weaning-off of propylene glycol, and in more severe cases following hemodialysis.

Medical monitoring is required.

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

Treatment
Treatment of overdosage is mainly supportive including monitoring of vital signs and close observation of the patient. An adequate airway should be maintained and assisted respiration used as needed. Hypotension, though unlikely, may be controlled with noradrenaline. Lorazepam is poorly dialysable.

The benzodiazepine antagonist, flumazenil, may be useful in hospitalised patients for the management of benzodiazepine overdosage. Flumazenil product information should be consulted prior to use. The physician should be aware of a risk of seizure in association with flumazenil treatment, particularly in long-term benzodiazepine users and in tricyclic antidepressant overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: benzodiazepine derivatives, ATC code: N05BA06.

Lorazepam is a benzodiazepine with anxiolytic, sedative, hypnotic, anticonvulsant and muscle relaxant properties.

5.2 Pharmacokinetic properties

Absorption

Lorazepam is readily absorbed when given intramuscularly. Peak plasma concentrations occur approximately 60-90 minutes following intramuscular administration.

Biotransformation

Lorazepam is metabolised by a simple one-step process to a pharmacologically inactive glucuronide. There is minimal risk of accumulation after repeated doses, giving a wide margin of safety.

There are no major active metabolites.

Elimination

The elimination half-life is about 12-16 hours when given intramuscularly or intravenously.

5.3 Preclinical safety data

Lorazepam glucuronide, the major metabolite of lorazepam, has no demonstrable CNS activity in animals.

Carcinogenicity

No evidence of carcinogenic potential emerged in rats and mice during an 18-month study with oral lorazepam.

Mutagenicity

A study of the mutagenic activity of lorazepam on Drosophila melanogaster indicated that this agent was mutationally inactive.

Impairment of fertility

A pre-implantation study in rats was performed with oral lorazepam at a 20 mg/kg dose that showed no impairment of fertility.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Macrogol (polyethylene glycol)
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: 24 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

1ml solution in a Type I glass ampoule (2ml capacity) with a one-point-cut opening.

Box of 5 or 10 ampoules.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

Lorazepam Macure is slightly viscous when cool. It must be inspected visually for the presence of particles or discolouration prior to administration. It should not be mixed with other drugs in the same syringe.

Intramuscular administration
Dilution with an equal volume of diluent is recommended. The diluent should be 0.9% sodium chloride, 5% glucose or water for injections.

Intravenous administration
Lorazepam injection should always be diluted with an equal volume of one of the following diluents: 0.9% sodium chloride, 5% glucose or water for injection.

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

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

2400 Copenhagen NV

Denmark

8 MARKETING AUTHORISATION NUMBER(S)

PL 53749/0002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

13/08/2025

10 DATE OF REVISION OF THE TEXT

05/01/2026