SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Lorazepam Medo 4 mg/ml

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 solution, free from visible particles.

WARNING: RISKS FROM CONCOMITANT USE WITH OPIOIDS
• Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death [see section 4.4].
• Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.
• Limit dosages and durations to the minimum required. Follow patients for signs and symptoms of respiratory depression and sedation.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Lorazepam Medo 4 mg/ml 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.

Lorazepam Medo 4 mg/ml 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 Medo 4 mg/ml.

b) I.M. administration:
The optimal effect is reached by administrating 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 Medo 4 mg/ml 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.

Status epilepticus
Adults: 4 mg intravenously.
Elderly: The elderly may respond to lower doses; thus, half the normal adult dose may be sufficient.
Pediatric population (age 1 month and older): 0.1 mg/kg body weight intravenously. Maximum 4 mg/dose.

The infusion rate should 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.

Pediatric population
The use of Lorazepam Medo 4 mg/ml in children under 12 years is contraindicated (see section 4.3), except in the management of status epilepticus (see also sections 4.1, 4.3 and 4.4).

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 Medo 4 mg/ml is not recommended for use in patients with severe hepatic insufficiency. When Lorazepam Medo 4 mg/ml 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 intramuscular and intravenous 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 Medo 4 mg/ml 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 Medo 4 mg/ml is also contraindicated in patients with:
- sleep apnoea syndrome;
- severe respiratory insufficiency;
- known hypersensitivity to benzodiazepines;
- myasthenia gravis;
- severe hepatic insufficiency.

Lorazepam Medo 4 mg/ml is contraindicated in children under 12 years of age, except in the control of status epilepticus.

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 Medo 4 mg/ml or use a reduced dose. Alcoholic beverages should not be used for at least 24 to 48 hours after receiving Lorazepam Medo 4 mg/ml, 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, except in the management of status epilepticus (see sections 4.1, 4.2 and 4.3).
After administration of lorazepam especially in neonates with very low birth weight, epileptic seizures and myoclonus were reported.

This medicinal product contains benzyl alcohol and propylene glycol (see below in “Information on excipients”).
Children may be sensitive to the other ingredients of this medicinal product: benzyl alcohol and propylene glycol. Benzyl alcohol may cause toxic reactions or anaphylactoid reactions in infants and children up to 3 years of age (see section 4.3).

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.

Information on excipients
Benzyl alcohol
This medicine contains 21 mg benzyl alcohol in each 1 ml of solution for injection (see section 2). Benzyl alcohol may cause allergic reactions.

Intravenous administration of benzyl alcohol has been associated with serious adverse events and death in neonates ("gasping syndrome"). 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 amount of benzyl alcohol at which toxicity may occur is not known.

Premature and low birth weight neonates are more likely to develop toxicity. Formulations containing benzyl alcohol should not be used for more than 1 week in children under 3 years of age, unless necessary.

If the use of this medicine is necessary, it is important to take into account the combined daily metabolic burden of benzyl alcohol from all sources. 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 (see section 2).

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

Prolonged administration of products containing propylene glycol, as well as co-administration with other substrates of alcohol dehydrogenase (e.g., ethanol), increase the risk of propylene glycol accumulation and toxicity, especially in patients with impaired hepatic or renal function.

The population predisposed to propylene glycol accumulation and associated potential adverse events include patients with an impaired alcohol and aldehyde dehydrogenase enzyme system, including pediatric patients less than 5 years of age, pregnant women, patients with severe renal or hepatic disease, and those receiving treatment 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 medicines containing propylene glycol or alcohol.

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

4.5. Interactions 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 Medo 4 mg/ml should only be used during pregnancy if strictly necessary for a period as short as possible and at the lowest possible dose.

This medicinal product contains benzyl alcohol and propylene glycol (see section 4.4 "Information on excipients"). Benzyl alcohol can cross the placenta. Propylene glycol has not been shown to cause reproductive or developmental toxicity in animals or humans, but propylene glycol 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.

Breastfeeding
Lorazepam passes in small amounts into breast milk. During Lorazepam Medo 4 mg/ml use, breastfeeding is not recommended.

This medicinal product 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 and may be taken orally by a breastfed child. Propylene glycol has not been shown to cause reproductive or developmental toxicity in animals or humans, but propylene glycol passes into breast milk and may be taken by mouth by a breastfed infant. Administration of ≥50 mg/kg/day of propylene glycol to breast-feeding women should only be considered on a case-by-case 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

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 (≥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 (≥ 1/10)*	*Common (≥1/100 to <1/10)*	*Uncommon (≥1/1,000 to <1/100)*	*Rare (≥1/10,000 to <1/1,000)*
Blood and lymphatic system disorders				Blood dyscrasia

System Organ Class	*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)*
Psychiatric disorders			Confusion, depression, emotional flattening, sleep disorders, change in libido	Temporary anterograde amnesia or memory disorder, paradoxical reactions*
Nervous system disorders		Sedation, drowsiness, dizziness, ataxia	Headache, decreased alertness	
Eye disorders			Visual disturbances, diplopia	
Vascular disorders				Hypotension, hypertension
Gastrointestinal disorders			Nausea, gastrointestinal symptoms	
Hepatobiliary disorders				Abnormal liver function tests
Skin and subcutaneous tissue disorders			Allergic skin reactions	
Musculoskeletal and connective tissue disorders		Muscle weakness		
General disorders and administration site conditions	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 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.
Any suspected adverse events should be reported to the Ministry of Health
according to the National Regulation by using an online form
https://sideeffects.health.gov.il

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.
This medicinal product contains propylene glycol. Various side effects have been reported with high doses (500 mg/kg/day or more) or prolonged use of propylene glycol, such as hyperosmolality, lactic acidosis; impaired renal function (acute tubular necrosis), acute renal failure; cardiotoxicity (arrhythmia, hypotension); disorders of the central nervous system (depression, coma, seizures); respiratory depression, dyspnea; impaired liver function; hemolytic reaction (intravascular hemolysis) and hemoglobinuria; or multi-organ failure. Such exposure can be achieved if the dose of the product significantly exceeds the recommended dose. 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
After intravenous administration, the mean volume of distribution is approximately 1.3 litres/kg. Unbound lorazepam crosses the blood-brain barrier unimpeded via passive diffusion. Lorazepam is approximately 92% bound to human plasma proteins at a lorazepam concentration of 160 ng/ml.

Biotransformation
Lorazepam is metabolized to a pharmacologically inactive glucuronide by a simple one-step process. There is a minimal risk of accumulation after repeated doses, providing a wide margin of safety. The total clearance of lorazepam after intravenous dose is approximately 1.0-1.2 ml/min/kg.
Lorazepam has 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; other hepatic and extrahepatic UGT enzymes also metabolized both R- and S-lorazepam *in vitro*.

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.
Following a single 2 mg and 4 mg intravenous lorazepam dose 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
Pediatric population
Neonates (birth to 1 month of age): After a single intravenous dose of lorazepam of 0.05 mg/kg (n=4) or 0.1 mg/kg (n=6), mean total clearance was normalized to body weight by 80% decreased relative to normal adults, terminal half-life increased 3-fold, and volume of distribution in neonates with neonatal asphyxia decreased 40% relative to normal adults. All neonates had a gestational age of $\geq$ 37 weeks.
There was no significant age-related difference in body weight normalized clearance in children, adolescents and adults, observed in 50 children aged 2.3-17.8 years. Population pharmacokinetic analyzes in children (excluding neonates) also indicate similar pharmacokinetics in adults.

Elderly

After single intravenous doses of lorazepam of 1.5 to 3 mg per injection, the mean total body clearance of lorazepam was reduced by approximately 20% in elderly subjects relative to younger adults.

Gender
Gender has no effect on the pharmacokinetics of lorazepam.

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.

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

5.3. Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Propylene glycol
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

The expiry date of the product is indicated on the packaging materials.

Stability after dilution:
Chemical and physical in-use stability has been demonstrated for 1 hour at 2-8ºC. 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 original package 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 Medo 4 mg/ml 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 Medo 4 mg/ml 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, 5% glucose or water for injection.
Lorazepam Medo 4 mg/ml can be also administered undiluted, if given deeply in a large muscle mass.

Intravenous administration:
In case of intravenous administration, Lorazepam Medo 4 mg/ml should always be diluted with an equal volume with sodium chloride 9 mg/ml (0.9%) solution for injection, 5% glucose or 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 Medo 4 mg/ml 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 Medo 4 mg/ml 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

A.L. Medi-Market, 3 Hakatif street, Emek Hefer Industrial Park, 3877701

8. MARKETING AUTHORISATION NUMBER

178-14-37646-99

9. MANUFACTURER

Medochemie Ltd., 1-10 Constantinoupoleos Street, 3011, Limassol, Cyprus

Approved in November 2024