LORANS – PACKAGE INSERT

1. NAME OF THE MEDICINAL PRODUCT

Lorans 1mg tablets
Lorans 2mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Lorans 1mg tablets contain 1 mg of lorazepam.
Lorans 2mg tablets contain 2 mg of lorazepam.

Excipient with known effect: lactose monohydrate.
For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Tablet
Lorans 1mg tablets are white, round, flat, scored tablet with diameter of 7mm
Lorans tablet 1mg can be divided into equal doses.

Lorans 2mg tablets are white, round, flat, scored, with diameter of 8mm, embossed with '2'
The score line is not intended for breaking Lorans 2mg tablet.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Lorans is indicated for the short term treatment of unacceptable disabling or distressful anxiety states including anxiety associated with psychosomatic, organic and psychotic illness, and the short term treatment of insomnia associated with anxiety.

4.2. Posology and method of administration

Dosage and duration of therapy should be individualised. The lowest effective dose should be prescribed for the shortest time possible. The risk of withdrawal and rebound phenomena is greater after abrupt discontinuation; therefore, the drug should be discontinued gradually for all patients (see section 4.4). Generally, the duration of treatment varies from a few days to 4 weeks including the tapering off process. Extension of the treatment period should not take place without re-evaluation of the need for continued therapy.

Increases in the dosage of lorazepam should be made gradually to help avoid adverse effects. The evening dose should be increased before the daytime doses.

Lorans tablets are for oral administration only.

Dosage:
Adults:

Moderate and severe anxiety:	1-4mg daily in divided doses
Insomnia:	1-2mg before retiring

Elderly and debilitated patients:
Elderly and debilitated patients may respond to lower doses and half the normal adult dose or less may be sufficient. This initial dose should be adjusted as needed and tolerated.

Children (aged 5-13 years):
Premedication: 0.5-2.5mg at 0.05mg/kg to the nearest 0.5mg according to weight, not less than one hour before operation.
Lorans is not recommended for the treatment of anxiety or insomnia in children.

4.3. Contraindications

Hypersensitivity to benzodiazepines including Lorans Tablets or to any other component of the formulation.
Severe respiratory insufficiency
Sleep apnoea syndrome
Myasthenia gravis

Severe hepatic insufficiency

4.4. Special warnings and precautions for use

Anaphylaxis (severe allergic reaction) and angioedema (severe facial swelling) which can occur as early as the first time the product is taken Complex sleep – related behaviours which may include sleep driving, making phone calls, preparing and eating food while asleep

Use of benzodiazepines, including lorazepam, may lead to potentially fatal respiratory depression.
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.
Lorazepam should be used with caution in patients with compromised respiratory function (e.g., COPD, sleep apnoea syndrome).
Patients should be advised that since their tolerance for alcohol and other CNS depressants will be diminished in the presence of lorazepam, these substances should either be avoided or taken in reduced dosage.
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.
Abuse of benzodiazepines has been reported, especially in patients with a history of drug and/or alcohol abuse.

Risks from Concomitant Use with Opioids
Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Lorans with opioids. Observational studies have demonstrated that concomitant use of opioids and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.
If the decision is made to newly prescribe a benzodiazepine and an opioid together, prescribe the lowest effective dosages and minimum durations of concomitant use.
If the decision is made to prescribe a benzodiazepine in a patient already receiving an opioid, prescribe a lower initial dose of the benzodiazepine than indicated in the absence of an opioid, and titrate based on clinical response.
If the decision is made to prescribe an opioid in a patient already taking a benzodiazepine, prescribe a lower initial dose of the opioid, and titrate based on clinical response.
Follow patients closely for signs and symptoms of respiratory depression and sedation. Advise both patients and caregivers about the risks of respiratory depression and sedation when Lorans is used with opioids. Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the opioid have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of opioids (See 4.5.Interactions with other medicinal products and other forms of interaction).

Tolerance
Some loss of efficacy to the hypnotic effects of short-acting benzodiazepines may develop after repeated use for a few weeks.
There is evidence that tolerance develops to the sedative effects of benzodiazepines.
Lorazepam may have abuse potential, especially in patients with a history of drug and/or alcohol abuse.

Dependence
The use of benzodiazepines may lead to physical and psychological dependence. The risk of dependence on Lorans is low when used at the recommended dose and duration, but increases with higher doses and longer term use. The risk of dependence is further increased in patients with a history of alcoholism or drug abuse, or in patients with significant personality disorders. Therefore, use in individuals with a history of alcoholism or drug abuse should be avoided.
Dependence may lead to withdrawal symptoms, especially if treatment is discontinued abruptly. Therefore, the drug should always be discontinued gradually.
Withdrawal symptoms (e.g. rebound insomnia) can appear following cessation of recommended doses after as little as one week of therapy. Abrupt termination of treatment may be accompanied by withdrawal symptoms.
Symptoms reported following discontinuation of benzodiazepines include headaches, muscle pain, anxiety, tension, depression, insomnia, restlessness, dizziness, nausea, diarrhoea, loss of appetite, confusion, hallucinations/delirium, perceptual changes, irritability, dysphoria, convulsions/seizures, tremor, abdominal cramps, myalgia, agitation, palpitations,

tachycardia, panic attacks, vertigo, hyperreflexia, short-term memory loss, hyperthermia, 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/perceptual changes, involuntary movements, vomiting, hallucinations, convulsions. Convulsions/seizures may be more common in patients with pre-existing seizure disorders or who are taking other drugs that lower the convulsive threshold such as antidepressants.

Duration
Treatment should be as short as possible. Generally, the duration of treatment varies from a few days to 4 weeks including the tapering off process.
It may be useful to inform the patient that treatment will be of limited duration and that it will be discontinued gradually. The patient should also be made aware of the possibility of "rebound" phenomena to minimise anxiety should they occur. There are indications that, in the case of benzodiazepines with a short duration of action, withdrawal phenomena can become manifest within the dosage interval, especially when the dosage is high.
When benzodiazepines with a long duration of action are being used it is important to warn against changing to a benzodiazepine with a short duration of action, as withdrawal symptoms may develop.

Amnesia
Transient anterograde amnesia or memory impairment has been reported in association with the use of benzodiazepines. This effect may be advantageous when Lorans is used as a premedicant. However, if Lorans is used for insomnia due to anxiety, patients should ensure that they will be able to have a period of uninterrupted sleep which is sufficient to allow dissipation of drug effect (e.g., 7-8 hours).

Psychiatric and paradoxical reactions
Paradoxical reactions have been occasionally reported during benzodiazepine use (see Undesirable Effects). Such reactions may be more likely to occur in children and the elderly. Should these occur, use of the drug should be discontinued.

Specific patient groups
Lorans 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. Therefore, large quantities of Lorans should not be prescribed to these patients. The use of benzodiazepines in these patients should not be used without adequate antidepressant therapy.
Pre-existing depression may emerge during benzodiazepine use.
Caution should be used in the treatment of patients with acute narrow-angle glaucoma.
Patients with impaired renal function or mild to moderate hepatic insufficiency 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.
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.
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.
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 should be warned of the risk of falls due to the myorelaxant effect of lorazepam.

Lorans contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5. Interactions with other medicinal products and other forms of interaction
Not recommended: Concomitant intake with alcohol
The sedative effects may be enhanced when the product is used in combination with alcohol. This affects the ability to drive or use machines.
The benzodiazepines, including lorazepam produce additive CNS depressant effects when co-administered with other medications which themselves produce CNS depression e.g., barbiturates, antipsychotics, sedatives/hypnotics, anxiolytics, antidepressants, narcotic analgesics, sedative antihistamines, anticonvulsants, and anaesthetics.

An enhancement of the euphoria induced by narcotic analgesics may occur with benzodiazepine use, leading to an increase in psychic dependence.
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.
There have been reports of excessive stupor, significant reduction in respiratory rate and, in one patient, hypotension when lorazepam and loxapine have been given concomitantly.
There have been reports of marked sedation, excessive salivation, and ataxia when lorazepam and clozapine have been given concomitantly.
Concurrent administration of lorazepam with sodium valproate may result in increased plasma concentrations and reduced clearance of lorazepam. Lorazepam dosage should be reduced to approximately 50% when coadministered with sodium valproate.
Concurrent administration of lorazepam with probenecid may result in a more rapid onset or prolonged effect of lorazepam due to increased half-life and decreased total clearance. Lorazepam dosage needs to be reduced by approximately 50% when coadministered with probenecid.
Administration of theophylline or aminophylline may reduce the sedative effects of benzodiazepines, including lorazepam.

Opioids
Due to additive pharmacologic effect, the concomitant use of opioids with benzodiazepines increases the risk of respiratory depression, profound sedation, coma and death.
The concomitant use of opioids and benzodiazepines increases the risk of respiratory depression because of actions at different receptor sites in the central nervous system that control respiration. Opioids interact primarily at μ-receptors, and benzodiazepines interact at GABAA sites. When opioids and benzodiazepines are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists.
Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate (see Warnings and Precautions).
Limit dosage and duration of concomitant use of benzodiazepines and opioids, and follow patients closely for respiratory depression and sedation.

4.6. Fertility, pregnancy and lactation
Benzodiazepines should not be used during pregnancy, especially during the first and last trimesters. Benzodiazepines may cause foetal damage when administered to pregnant women. In particular, an increased risk of congenital malformations associated with the use of benzodiazepines during the first trimester of pregnancy has been suggested in several studies. In humans, umbilical cord blood samples indicate placental transfer of benzodiazepines and their glucuronide metabolites.
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.
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 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, hypoactivity, 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 is evidence that lorazepam is excreted, albeit in pharmacologically insignificant amounts, in human breast milk. Therefore, Lorans should not be given to breastfeeding mothers unless the expected benefit to the mother outweighs the potential risk to the infant. Sedation and inability to suckle have occurred in neonates of lactating mothers taking benzodiazepines. Infants of lactating mothers should be observed for pharmacological effects (including sedation and irritability).

4.7. Effects on ability to drive and use machines
Sedation, amnesia, impaired concentration and impaired muscular function may adversely affect the ability to drive or to use machines. If insufficient sleep occurs, the likelihood of impaired alertness may be increased (see also interactions). Patients should be warned not to operate dangerous machinery or motor vehicles if any of these effects occur.

4.8. Undesirable effects
Adverse reactions, when they occur, are usually observed at the beginning of therapy and generally decrease in severity or disappear with continued use or upon decreasing the dose.
Adverse reactions are listed in the following table in CIOMS frequency categories:

Body as a whole	
Frequency not known	Hypersensitivity reactions, anaphylactic/anaphylactoid reactions, angioedema, SIADH, hyponatraemia, hypothermia
Common	Muscle weakness, asthenia
Cardiovascular:	
Frequency not known	Hypotension, lowering in blood pressure
Digestive:	
Uncommon:	Nausea
Frequency not known:	Constipation, increase in bilirubin, jaundice, increase in liver transaminases, increase in alkaline phosphatase
Haematological/lymphatic:	
Frequency not known	Thrombocytopenia, agranulocytosis, pancytopenia
Nervous system and special senses:	
Frequency not known	Benzodiazepine effects on the CNS are dose dependent, with more severe CNS depression occurring with high doses Extrapyramidal symptoms, tremor, vertigo, visual disturbances (including diplopia and blurred vision), dysarthria/slurred speech, headache, convulsions/seizures; amnesia, disinhibition, euphoria, coma, suicidal ideation/attempt, impaired attention/ concentration, balance disorder Paradoxical reactions including anxiety, agitation, excitation, hostility, aggression, rage, sleep disturbances/insomnia, sexual arousal, hallucinations
Very common:	Sedation, fatigue, drowsiness
Common:	Ataxia, confusion, depression, unmasking of depression, dizziness
Uncommon:	Change in libido, impotence, decreased orgasm
Respiratory:	
Frequency not known	Respiratory depression, apnoea, worsening of sleep apnoea (the extent of respiratory depression with benzodiazepines is dose dependent, with more severe depression occurring with high doses) Worsening of obstructive pulmonary disease
Skin:	
Frequency not known	Allergic skin reactions, alopecia

Pre-existing depression may emerge during benzodiazepine use.
Transient anterograde amnesia or memory impairment may occur using therapeutic doses, the risk increasing at higher doses (see section 4.4 Warnings & Precautions).
Paradoxical reactions such as restlessness, agitation, irritability, aggressiveness, delusion, rage, nightmares, hallucinations, psychoses, and inappropriate behaviour have been occasionally reported during benzodiazepine use. Such reactions may be more likely to occur in children and the elderly (see section 4.4 Warnings & Precautions).
Use (even at therapeutic doses) may lead to physical or psychological dependence and discontinuation of treatment may result in withdrawal reactions or rebound phenomena (see section 4.4 Warnings & Precautions).

4.9. Overdose
In the management of overdosage with any drug, it should be borne in mind that multiple agents may have been taken. In postmarketing experience, overdose with lorazepam has occurred predominantly in combination with alcohol and/or other drugs.
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 dysarthria, ataxia, paradoxical reactions, CNS depression, hypotension, hypotonia, respiratory depression, cardiovascular depression, coma, and very rarely, death.
When there is a risk of aspiration, induction of emesis is not recommended. If ingestion was recent, induced vomiting and/or gastric lavage should be undertaken followed by general supportive care, monitoring of vital signs and close observation of the patient. If there is no advantage in emptying the stomach, activated charcoal may be effective in reducing absorption. Hypotension, though unlikely, may be controlled with noradrenaline. Lorazepam is poorly dialysable. Lorazepam glucuronide, the inactive metabolite, may be highly dialysable.
The benzodiazepine antagonist, flumazenil may be useful in hospitalised patients as an adjunct to, not as a substitute for, proper management of benzodiazepine overdose. 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 cyclic antidepressant overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Benzodiazepine derivatives, Anxiolytics ATC code: N05BA06.

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

5.2. Pharmacokinetic properties

Lorazepam is almost completely absorbed from the gastrointestinal tract and peak serum levels are reached in 2 hours. It is metabolised by a simple one-step process to a pharmacologically inert glucuronide. There are no major active metabolites. The elimination half-life is about 12 hours and there is minimal risk of excessive accumulation. At clinically relevant concentrations, lorazepam is approximately 90% bound to plasma proteins.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lorans 1mg tablets also contain:
- lactose monohydrate,
- microcrystalline cellulose,
- croscarmellose sodium,
- magnesium stearate.

Lorans 2mg tablets also contain:
- lactose monohydrate,
- microcrystalline cellulose,
- sodium croscaramellose,
- magnesium stearate.

6.2. Incompatibilities

No known incompatibilities.

6.3. Shelf life

2 years

6.4. Special precautions for storage

Store below 25°C, in the original package.

6.5. Nature and contents of container

Lorans tablets (1mg and 2mg) are packed in aluminium foil-PVC film blisters, with a patient information leaflet, in a card carton. Packs containing 1000 tablets are available.

6.6. Special precautions for disposal

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

7. Marketing Authorisation Holder:

Komedic Sdn Bhd, 4 Jalan PJS 11/14, Bandar Sunway, 46150 Petaling Jaya

8. Manufacturer:

Lorans 1mg tablets: Medochemie Ltd. (Factory AZ), 2 Michael Erakleous Street, Agios Athanassios Industrial Area, Agios Athanassios 4104, Limassol, Cyprus
Lorans 2mg tablets: Medochemie Ltd. (Central Factory), 1-10 Constantinoupoleos Street, 3011 Limassol, Cyprus

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Lorans 1mg tablets: 15/12/1986
Lorans 2mg tablets: 15/12/1986

10. DATE OF REVISION OF THE TEXT

12/2022