SUMMARY PRODUCT CHARACTERISTIC (SPC)

LORAZEPAM

1 mg and 2 mg tablets

1.1 BRAND NAME – LORAZEPAM

1.2 INTERNATIONAL NON-PROPERTY NAME - LORAZEPAM

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Lorazepam 1 mg tablet contains:
active ingredient: lorazepam - 1 mg
For a full list of excipients, see section 6.1.
Each Lorazepam 2 mg tablet contains:
active ingredient: lorazepam - 2 mg
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Lorazepam, 1 mg tablets
White or off white scored cylindrical tablets with a few small darker spots and with a risk on one side and a facet on both sides.
Lorazepam, 2 mg tablets
White scored cylindrical tablets with a risk on one side and a facet on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Lorazepam 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. Lorazepam may also be used as premedication before operative dentistry and general surgery.

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. 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 reevaluation 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.

Dosage:

Adults:

Moderate and severe anxiety:	1-4 mg daily in divided doses.
Insomnia:	1-2 mg before retiring
Premedication before operative dentistry or general	2-3 mg the night before operation
surgery:	2-4 mg one to two hours befor operation.

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.

Paediatric population **(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.

Lorazepam is not recommended for the treatment of anxiety or insomnia in children.

Patients with Renal or Hepatic impairment:

Lower doses may be sufficient in patients with impaired renal function or mild to moderate hepatic insufficiency (see section 4.4). Use in patients with severe hepatic insufficiency is contraindicated (see section 4.3).

Method of Administration:

Lorazepam tablets are for oral administration only.

4.3 Contraindications

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

Severe respiratory insufficiency

Sleep apnoea syndrome

Myasthenia gravis

Severe hepatic insufficiency

4.4 Special warnings and precautions for use

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.

Lorazepam tablets contains:

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

Tolerance

Some loss of efficacy to the hypnotic effects of shortacting 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 lorazepam 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, shortterm 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 preexisting 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 Ativan is used as a premedicant. However, if Lorazepam 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 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.

Specific patient groups

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. Therefore, large quantities of Lorazepam 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.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucosegalactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

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 coadministered 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 halflife 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.

4.6 Fertility, pregnancy and lactation

Pregnancy:

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.

Lactation:

There is evidence that lorazepam is excreted, albeit in pharmacologically insignificant amounts, in human breast milk. Therefore, Lorazepam 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 section 4.5**). 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:

Very common ≥10%

Common	≥1%
Uncommon	≥0.1% and <1%
Rare	≥0.01% and <0.1%
Very rare	<0.01%

Body as a whole:

Frequency undetermined: Hypersensitivity reactions, anaphylactic/anaphylactoid reactions, angioedema, SIADH, hyponatraemia, hypothermia

Common: Muscle weakness, asthenia

Cardiovascular:

Frequency undetermined: Hypotension, lowering in blood pressure

Digestive:

Uncommon: Nausea

Frequency undetermined: constipation, increase in bilirubin, jaundice, increase in liver transaminases, increase in alkaline phosphatase

Haematological/lymphatic:

Frequency undetermined: Thrombocytopenia, agranulocytosis, pancytopenia

Nervous system and special senses:

Frequency undetermined: 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 undetermined: 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 undetermined: 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).

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).

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).

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 Arpimed "LLC" by going to www.arpimed.com and fill out the appropriate form ″Report an adverse reaction or inefficiency of drug″. Hotline number: (+374 55) 05 79 86. And by using Scientific Centre of Drug and Medical Technology Expertise after academician E. Gabrielyan ″CJSC ″, going to the site: www.pharm.am in ″Report about adverse effect of medicine″ section and fill out the ″Report of adverse reaction or manufacturing problem of medicinal product″.
Hotline numbers: +37410237265; +37498773368.

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 longterm benzodiazepine users and in cyclic antidepressant overdose.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacological class: Benzodiazepine
Therapeutic class: Anxiolytic
ATC code: NO5BA06
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.

5.3 Preclinical safety data

Oesophageal dilation occurred in rats treated with lorazepam for more than one year at 6 mg/kg/day.

6. Pharmaceutical particulars

6.1 List of excipients

Lorazepam 1 mg and 2 mg tablets
microcrystalline cellulose
lactose monohydrate
maize (corn) starch
povidone
sodium starch glycolate
magnesium stearate
talc purified.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life
3 years.
Do not use this medicine after the expiry date.

6.4 Special precautions for storage
Lorazepam 1 mg tablets
Store at a temperature 15-25^{0}C, in a dry place, out of the reach of children. Protect from light.
Lorazepam 2 mg tablets
Store at a temperature 15-25^{0}C, in a dry place, out of the reach of children. Protect from light.

6.5 Nature and contents of container
Lorazepam 1 mg tablets
1 blister packet with 24 tablets with leaflet in the cardboard box.
Lorazepam 2 mg tablets
1 blister packet with 24 tablets with leaflet in the cardboard box.

6.6 Special precautions for disposal and other handling
No special requirements.

6.7. MANUFACTURER
"ARPIMED" LLC
Bldg. 19, mcr 2-nd, Abovyan, Kotayki Marz, Republic of Armenia
Tel.: (374) 222 21703 Fax: (374) 222 21924

6.8. MARKETING AUTHORIZATION HOLDER
"ARPIMED" LLC
Bldg. 19, mcr 2-nd, Abovyan, Kotayki Marz, Republic of Armenia
Tel.: (374) 222 21703 , Fax: (374) 222 21924

6.9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
Lorazepam 1 mg tablets- 19.09.2003
Lorazepam 2 mg tablets-13.02.2008

6.10. DATE OF REVISION OF THE TEXT