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)
Nervous system disorders ±	Sedation, drowsiness	Ataxia, dizziness		Extrapyramidal symptoms, tremor, dysarthria/slurred speech, headache, convulsions/seizures, amnesia, coma
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[β], apnea, worsening of sleep apnea, worsening of obstructive pulmonary disease
Gastrointestinal disorders			Nausea	Constipation
Hepatobiliary disorders				Jaundice
Skin and subcutaneous tissue disorders				allergic skin reactions, alopecia
Musculoskeletal and connective tissue disorders		Muscle weakness		
Reproductive system and breast disorders			Impotence	
General disorders and administration site conditions	Fatigue	Asthenia		Hypothermia
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
β The extent of respiratory depression with benzodiazepines is dose dependent, with more severe depression occurring with high doses.

Drug Interactions

The benzodiazepines, including Ativan, produce additive CNS deppresant effect when co-administered with other CNS depression such as alcohol, barbiturates, antipsychotics, sedative/hypnotics, anxiolytics, antidepressants, narcotic analgesics, sedative antihistamines, anticonvulsants, and anesthetics.

The concomitant use of sedative medicines such as benzodiazepines or related drugs such as 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.

The cytochrome P450 system has not been shown to be involved in the disposition of Ativan and, unlikely many benzodiazepines, pharmacokinetic interactions involving the P450 system have not been observed with Ativan.

No interference with laboratory tests has been identified or reported with the use of lorazepam.

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

Concurrent administration of lorazepam with valporate may result in increased plasma concentrations and reduced clearance of lorazepam. Lorazepam dosage should be reduced to approximately 50% when coadministered with 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 co administered with probenecid.

Administration of theophyilline or aminophyiline may reduce the sedative effects of benzodiazepines, including lorazepam.

Availability

ATIVAN is supplied as tablets 0.5 mg, 1 mg and 2 mg strengths.

ATIVAN tablet 0.5 mg - 10 strips of 10 tablets Reg.No. DPL8931800210A1
ATIVAN tablet 1 mg - 10 strips of 10 tablets Reg.No. DPL8931800210B1
ATIVAN tablet 2 mg - 10 strips of 10 tablets Reg.No. DPL8931800210C1

Store in dry place below 30º C

ON MEDICAL PRECRIPTION ONLY
HARUS DENGAN RESEP DOKTER

Manufactured & Sold by
PT SUNTHI SEPURI
Tangerang, Indonesia

Under license from
PT PFIZER INDONESIA
Jakarta, Indonesia

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Ativan* Tablet *(Antianxiety)*
lorazepam

Composition

Each Tablet Contain :
Lorazepam ..... 0.5 mg, 1.0 mg, 2.0 mg
Polacrilin Potasium, Magnesium Stearate, Microcrystalline cellulose,
Indigotine CI*, FD&C Yellow**, Lactose Monohydrate.

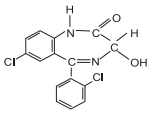
**Only used on Ativan 0.5 mg*
***Only used on Ativan 2.0 mg*

Appearance

0.5 mg : Round, flat, blue tablet, bisected line on one side and flat on the other side
1 mg : Round, flat, white tablet, bisected line on one side and flat on the other side
2 mg : Round, flat, yellow tablet, bisected line on one side and flat on the other side

Description

Lorazepam (Ativan), an antianxiety agen, is a 1,4-benzodiazepin designated is 7 - chloro - 5 - (o - chlorophenyl) - 1,3-dhydro - 3 - hydroxy - 2H - 1,4 - benzodiazepin- 2 - one. Its structural formula is :



Lorazepam is a nearly white powder which is almost insoluble in water and slightly soluble in alcohol and chloroform. The molecular weight 321.2.

Clinical Pharmacology

Ativan provides prompt relief from a variety of symptoms associated with anxiety and inanxiety associated with depression.

The exact mechanism of action of benzodiazepines has not yet been elucidated, however, benzodiazepines appear to work through several mechanisms. Benzodiazapines presumably exert their effects by binding to specific receptors at several sites within the central nervous system, either by potentiating the effects of synaptic or presynaptic inhibition mediated by gamma – aminobutyric acid directly affecting the action potential generating mechanisms.

Ativan is readly absorbed when given orally. Peak concentration in plasma occur approximately 2 hours following administration. The half-life of unconjugated Ativan in human plasma is approximately 12 – 16 hours. At clinically relevant concentrations. Ativan is approximately 90% bound to plasma proteins.

Conjugation with glucuronic acid to form the inactive glucuronide of Ativan is the major metablolic pathway. Seventy to seventy five percent of the dose is excreted as the glucuronide in the urine. The glucoronides of Ativan have no demonstrable CNS activities in animals, and there are no active metabolites of Ativan.

The plasma levels of Ativan are proportional to dose given. There is no evidence of excessive accumulation of Ativan on administration up to 6 month nor is there any indication of induction of drug-metabolizing enzymes under these conditions. Ativan is not a substrate for N-dealkylating enzymes of the cytochrome P450 system nor is it hydroxylated to any significant extent.

Studies comparing young and elderly subjects have shown that the pharmacokinetics of lorazepam remain unaltered with advancing age. No changes in absorption distribution, metabolism and excretion were reported in patients with hepatic diseases (hepatitis, alcoholic cirrhosis). As with other benzodiazepines, the pharmacokinetics of lorazepam may change in impaired renal function.

Indication and Usage

Ativan is indicated for :
1. Management of anxiety disorders or for the short term relief of the symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic. The physician should periodically reassess the usefulness of the drug for individual patient.
2. Psychoneurotic disorders including anxiety, depressive, obsessive compulsive, phobic or mixed reactions.
3. The anxiety component in psychotic states and severe depression where adjunctive therapy is indicated.
4. Pre-surgical medication taken the night before surgery and/or 1 – 2 hours prior to the surgical procedure.

Dosage and Administration

Ativan is administered orally. For optional result dose, frequency of administration and duration of therapy should be individualized according to patient response. Dosage should be individualized for maximum beneficial effect. In patients previously treated with anxiolytic agents, higher initial dosages of Ativan may be indicated.

The lowest effective dose should be prescribed for the shortest duration possible. The risk of withdrawal and rebound phenomena is greater after abrupt discontinuation ; therefore the drug should be discontinued gradually.

The average daily dosage for treatment of anxiety is 2 mg to 3 mg administered in divided doses, however this may range between 1 and 10 mg.
Children (6-12 years of age) respond to lower anxiolytic doses of Ativan.

Dosages higher than 10 mg daily have been successfully employed in hospitalized cases, especially as adjunctive therapy in psychosis and severe depression.

For insomnia due to anxiety or transient situational stress, a single daily dose of 1 – 2 mg may be given, usually at bedtime.

For elderly or debilitated patients, reduce the initial dose by approximately 50% and adjust the dosage as needed and tolerated.

For pre-surgical medication, a dosage of 2 – 4 mg Ativan is recommended the night before surgery and / or 1 – 2 hours prior to the surgical procedure.

Dosage for patients with severe hepatic insufficiency should be adjusted carefully according to patient response. Lower doses may be sufficient in such patients.

Overdosage

In post marketing experience, overdose with lorazepam has occurred predominantly in combination with alcohol and/or other drugs.

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

General supportive and symptomatic measures are recommended; vital signs must be monitored.

When there is a risk of aspiration, induction of emesis is not recommended. Gastric lavage may be indicated if performed soon after ingestion or in symptomatic patients. Administration of activated charcoal may also limit drug absorption. The value of dialysis has not been adequately determined for Ativan.

Over dosage of benzodiazepines is usually manifested by degrees of central nervous system depression ranging from drowsiness to coma. Symptoms can range in severity and include drowsiness, mental confusion, lethargy, dysarthria, paradoxical reactions, CNS depression, hypotonia, respiratory depression, and cardiovascular depression. In mild cases, symptoms included drowsiness, mental confusion and lethargy. In more serious case, symptoms may include ataxia, hypotension, hypnosis, stage one (1) to three (3) coma, and very rarely, death.

Published reports for some benzodiazepines indicates that intravenous infusion of 0.5 to 4 mg of physostigmine at the rate of 1 mg/minute may reverse symptoms and signs suggestive of central anticholinergic overdose (confusion, memory disturbance, visual disturbances, hallucinations, delirium), however, hazards associated with the use of physostigmine (i.e. induction of seizures) should be weighed against its possible clinical benefit . In addition , extreme caution should be employed in the use of physostigmine when bradycardia and/or hypotension is present.

Lorazepam is poorly dialyzable. Lorazepam glucuronide, the inactive metabolite, may be highly dialyzable.

The benzodiazepine antagonist flumazenil may be used in hospitalized patients as an adjunct to, not as a substitute for, proper management of benzodiazepine overdose. 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.

Contraindications

Ativan is contraindicated in patients with a known hypersensitivity to benzodiazepines or to any components of the formulation.

Warnings

As with all patients on CNS-depressant drugs, patients receiving Ativan should be warned not to operate dangerous machinery or motor vehicles until it is known that they do not become drowsy or dizzy from lorazepam therapy. Patients should be advised that their tolerance for alcohol and other CNS depressants will be diminished and should either be eliminated or given in reduced dosage in the presence of lorazepam.

Ativan is not intended for the treatment of primary depressive disorders or for the primary treatment of psychosis. It is recommended that the need for continued therapy with Ativan be determined periodically.

Use of benzodiazepines, including lorazepam, may lead to potentially fatal respiratory depression.

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. 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.

The use of benzodiazepines, including lorazepam, may lead to pyshical and psychological dependence.

Precautions

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

The usual precautions for treating patients with impaired renal or hepatic function should be observed.

Transient amnesia or memory impairment has been reported in association with the use of benzodiazepines.

Some patients on benzodiazepines have developed blood dyscrasias, and some have had elevations in liver enzymes. As with other benzodiazepines, periodic blood count and liver-function tests are recommended for patients on long-term therapy.

Lorazepam should be used with caution in patients with compromised respiratory function (eg, COPD, sleep apnea syndrome).

Pre-existing depression may emerge or worsen during use of benzodiazepines including lorazepam.

The use of benzodiazepines may unmask suicidal tendencies in depressed patients and should not be used without adequate antidepressant therapy.

Elderly or debilitated patients may be more susceptible to the effects of lorazepam; therefore, these patients should be monitored frequently and have their dosage adjusted carefully according to patient response.

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

As with all benzodiazepines, the use of lorazepam may worsen hepatic encephalopathy; therefore, lorazepam should be used with caution in patients with severe hepatic insufficiency and/or encephalophaty.

Carcinogenesis, Mutagenesis, impairment of Fertility. No evidence of carcinogenic potential emerged in rats or mice during an 18-month study with oral Ativan. An investigation of the mutagenic activity of Ativan on Drosphila melanogaster indicated that this agent was multationally inactive.
A pre-implanation study in rats was performed with oral Ativan at a 20 mg/kg dose which showed no impairment of fertility.
Use During Pregnancy-Lorazepam should not be used during pregnancy. Benzodiazepines may cause fetal damage when administered to pregnant women. An increased risk of congenital malformations associated with the use of anxiolytic agents (chlordiazepoxide, diazepam, and meprobamate) has been suggested in several studies.

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 hypo activity, hypotonia hypothermia, respiratory depression, apnea, 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.

The use, therefore, of benzodiazepines during the first trimester of pregnancy should almost always be avoided. If the drug is prescribed to a woman of child-bearing potential, she should be warned to contact her physician regarding discontinuation of the drug if she intends to become or suspects she is pregnant.

In humans, blood levels obtained from umbilical cord indicate placenta transfer of Ativan and its glucronide. Neonates appear to conjugate Ativan slowly, the glucuronide being detectable in the urine for more than seven days. Glucuronidation of Ativan may competitively inhibit the conjugation of bilirubin, leading to hyperbilirubinemia in the newborn.

The use of Ativan during the late phase of pregnancy or at delivery may require ventilation of the infant at birth.

Use During Lactation-Caution should be exercised when Ativan is given to nursing women since there is evidence that Ativan is excreted, in pharamacologically insignificant amounts, in human breast milk. Ativan should not be administered to breast-feeding women, unless the expected benefit to the woman outweighs the potential risk to the infant.

Sedation an 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).

Pediatric Use-Ativan is not recommended for use in children less than 6 years of age. Avoid long term treatment because it will cause physical and physical dependence.
Drug Abuse and Dependence

Drug Abuse & Dependence

Abuse

Addiction-prone individuals, such as drug addicts and alcoholics, should be under careful surveillance when receiving benzodiazepines because of the predisposition of such patients to habituation and dependence.

Dependence

The use of benzodiazepines may lead to physical and psychological dependence. Withdrawal symptoms similar in character to those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines drug after as little as one week of therapy. Symptoms reported following discontinuation of benzodiazepines include headache, anxiety, tension, depression, insomnia, restlessness, confusion, irritability, sweating, rebound phenomena, dysphoria, dizziness, de realization, depersonalization, hypercausis, numbness/tingling of extremities, hypersensitivity to light, noise, and physical contact/perceptual changes, involuntary movements, nausea, vomiting, diarrhea, loss of appetite, hallucination/delirium, convulsions/seizures, tremor, abdominal cramps, myalgia, agitation, palpitations, tachycardia, panic attacks, vertigo, hyperreflexia, short-term memory loss, and hyperthermia.

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 antidepressant. These symptoms, especially the more serious ones, are more common in those patients who have received excessive doses over an extended period of time and is further increased in patients with a history of alcoholism or drug abuse or in patients with significant personality disorders. The dependences potential is reduced when lorazepam is used at the appropriate dose for short-term treatment. In general, benzodiazepines should be prescribed for short periods only (eg, 2-4 weeks). Continuous long-term use of lorazepam is not recommended.

However, withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels. Accordingly, Ativan should be terminated gradually to help avoid occurrence of withdrawal symptoms.

There is evidence that tolerance develops to the sedative effects of benzodiazepines.

Adverse Reactions

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		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 arousal, hallucinations