Lorazepam Tablets I.P.

Ativan® Tablets

1. GENERIC NAME

Lorazepam Tablets I.P.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated tablet contains: Lorazepam I.P. 1 mg.
Each uncoated tablet contains: Lorazepam I.P. 2 mg.

List of Excipients

Lorazepam 1 mg tablet: Lactose I.P., Microcrystalline Cellulose I.P., Maize Starch Special Qlty NBS, Magnesium Stearate I.P.

Lorazepam 2 mg tablet: Lactose I.P., Microcrystalline Cellulose I.P., Maize Starch Special Qlty NBS, Lake Sunset yellow, Magnesium Stearate I.P.

All strengths/presentations mentioned in this document might not be available in the market.

3. DOSAGE FORM AND STRENGTH

Uncoated tablets of Lorazepam 1 mg and 2 mg.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indication

Short-term management of anxiety disorders, including the following:
- Short-term relief of symptoms of anxiety
- Generalized anxiety disorders
- Anxiety in psychotic states
- Anxiety associated with somatic symptoms
- Anxiety associated with depression or depressive symptoms
- Reactive anxiety
- Insomnia associated with anxiety
- Alcohol withdrawal
- Prevention of delirium tremens

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- Adjunctive therapy to standard antiemetic drugs for the prophylactic and symptomatic treatment of nausea and vomiting associated with cancer chemotherapy
- Surgical premedication

4.2 Posology and Method of Administration

Dosage and duration of therapy has to be individualized depending on symptoms and underlying condition. The risk of dependence may increase with dose and duration of treatment; therefore the lowest effective dose should be prescribed for the shortest duration and the need for continued treatment reassessed frequently (see section 4.4).

Abrupt discontinuation or rapid dosage reduction of lorazepam after continued use may precipitate withdrawal reactions which can be life threatening and/or rebound phenomena; therefore, the drug should be discontinued gradually or reduce the dosage (see section 4.4).

Duration of Treatment

Indication should be reviewed after several months with continuous use.

The duration of use must be as short as possible. Considering the gradual discontinuation of treatment, duration of treatment must not exceed 4 weeks for sleep disorders and 8 - 12 weeks for anxiety.

Posology

Adults
Anxiety: with outpatient treatment 1-3 mg lorazepam in several divided daily doses will generally be sufficient.

Sleep disorders: Usually 1 mg lorazepam about ½ hour before bedtime.

Pediatric population (younger than 6 years)
See section 4.3.

Pediatric population (6-18 years)
As no data on safety and efficacy in this age group is available, lorazepam is not recommended for use in children and juveniles.

Elderly and debilitated patients
For elderly and debilitated patients the overall initial daily dosage has to be reduced by about 50% and then adjusted according to the required efficacy and as individually tolerated (see section 4.4).

Patients with hepatic impairment
In patients with hepatic dysfunction dosage must be carefully adjusted to their reaction. Lower doses or a prolonged dosing interval may be sufficient for such patients (see section 4.4).

In patients with severe hepatic dysfunction use of lorazepam is contraindicated (see section 4.3).

Patients with renal impairment
There is no particular recommendation for dosage in patients with renal dysfunction.

Method of administration

For oral use.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 2
- Hypersensitivity to other benzodiazepines
- Myasthenia gravis
- Acute intoxication with alcohol or psychotropic substances
- Children younger than 6 years
- Sleep apnea syndrome
- Severe hepatic insufficiency
- Severe respiratory insufficiency

4.4 Special Warnings and Precautions for Use

Hypersensitivity reactions

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 dyspnea, throat closure 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 paragroup allergy.

Patients with respiratory depression

Use of benzodiazepines, including lorazepam, may lead to potentially fatal respiratory depression. Therefore, lorazepam should be used with caution in patients with impaired respiratory function (e.g. COPD) (see section 4.3).

Concomitant use of opioids

Concomitant use of lorazepam and opioids may result in profound 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, limit dosages and durations to the minimum required. (see also general 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).

Psychic and paradoxical reactions

Paradoxical reactions have occasionally been described with the use of benzodiazepines (see also section 4.8). Such reactions must be expected, especially in children and elderly persons. When paradoxical reactions occur, treatment with lorazepam should be discontinued.

Patients with depression

Pre-existing depression may emerge or worsen during use of benzodiazepines, including lorazepam. The use of benzodiazepines may unmask suicidal tendency in depressed patients and should not be used without adequate antidepressant therapy.

The possibility of suicide should be considered and, therefore, no larger amounts of lorazepam should be prescribed.

Lorazepam tablets are not intended for the treatment of endogenous depression or psychotic disorders, unless when used temporarily as adjunctive medication in patients with concurrent anxiety conditions or insomnia, if these cannot adequately controlled with antidepressants or neuroleptics.

Patients with circulation disorders

In patients with cerebral perfusion disorders or reduced general condition an increased response to the drug must be anticipated which may be accounted for by cautious dosing. Although blood pressure drop was only seen in rare instances, benzodiazepines should be used with caution in patients in whom a blood pressure drop could lead to cardiovascular or cerebrovascular complications.

Convulsions

In patients with Lennox-Gastaut syndrome, benzodiazepines may cause tonic-clonic convulsions. This should be considered for treatment with Lorazepam tablets.

Concomitant use of other tranquilizers

Patients should be advised that tolerability of other tranquilizers may be reduced and these should either be discontinued or given at lower dosage when using lorazepam.

Elderly patients

Reduced attention, e.g. in elderly or debilitated patients, as a result of surgery or poor general condition may persist for prolonged periods.

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 or debilitated patients may show a more sensitive response to the effects of

lorazepam; therefore, these patients should be more frequently monitored and given a reduced dose (see section 4.2).

Amnesia

Benzodiazepines may trigger anterograde amnesia mostly occurring few hours after administration.

Long-term treatment

It is recommended to verify the need for continued treatment with lorazepam tablets at regular intervals.

As a precaution regular controls of blood counts and hepatic function are recommended in long-term treatment with benzodiazepines as blood dyscrasia and increased hepatic enzymes have been reported (see also section 4.8).

Patients with hepatic impairment

As with all benzodiazepines, the use of lorazepam may worsen a hepatic encephalopathy; therefore, lorazepam should be used with caution in patients with hepatic insufficiency and/or encephalopathy (severe hepatic dysfunction, see section 4.3).

Patients with gastrointestinal and cardiovascular disorders

In patients with gastrointestinal and cardiovascular disorders and concomitant anxiety states no significant benefit could be seen for lorazepam tablets in the treatment of these underlying conditions. Caution is indicated when using lorazepam tablets for prolonged period or in elderly and debilitated patients. The upper GI tract should be regularly monitored for disturbances.

Tolerance

Development of tolerance to the sedative effects of benzodiazepines is possible.

Dependence

The use of benzodiazepines, including lorazepam, may lead to physical and psychological dependence. The risk of dependence is low when the guidelines for dosing and short duration of use are considered, but it will increase with dose level and duration of use and is also increased in patients with a history of known alcohol dependence or alcohol abuse or in patients with significant personality disorders. The dependence potential is reduced when lorazepam is used at the appropriate dose for short-term treatment.

Withdrawal Reactions

Withdrawal symptoms, in particular severe symptoms, are seen at higher frequency in those patients given high doses for prolonged periods. Withdrawal symptoms (e.g. recurrent insomnia) may occur upon discontinuation of use after only one week of use at the recommended dose. Abrupt termination of treatment with lorazepam should be avoided. In order to avoid withdrawal

symptoms, the dose of lorazepam tablets should be gradually reduced after prolonged treatment. Patients should be instructed to consult their doctor before either reducing the dose or abruptly discontinuing the drug by themselves. Generally, benzodiazepines should only be prescribed for short periods (e.g. 2 – 4 weeks). Continual use over prolonged periods is not recommended.

Abrupt discontinuation or rapid dosage reduction of lorazepam after continued use may precipitate withdrawal reactions, which can be life threatening. These can range from mild dysphoria and insomnia to a major syndrome which may include abdominal and muscle cramps, vomiting, sweating, tremor, and convulsions. More severe acute withdrawal signs and symptoms, including life-threatening reactions, have included delirium tremens, depression, hallucinations, mania, psychosis, seizures, and suicidality. Convulsions/seizures may occur more often in patients with preexisting seizure disorders or in patients who take other drugs that lower the convulsive threshold, such as antidepressants.

The following symptoms have also been described: headache, anxiety, tension, restlessness, confusion and irritability, rebound phenomena, dysphoria, dizziness, derealization, depersonalization, hyperacusis, tinnitus, tingling and numbness in extremities, increased sensitivity to light, noise and physical contact/perceptual changes, involuntary movements, nausea, lack of appetite, diarrhea, panic attacks, myalgia/muscle pain, agitation, palpitation, tachycardia, vertigo, hyperreflexia, short term memory loss, and hyperthermia. Upon abrupt discontinuation of benzodiazepines similar withdrawal symptoms were encountered as seen after withdrawal of barbiturates and alcohol.

Rebound phenomenon, insomnia and anxiety: a transient syndrome resulting in an increased recurrence of symptoms having been the original reason for treatment with benzodiazepines and potentially recurring upon discontinuation of treatment. It may be accompanied by other reactions such as mood fluctuations, anxiety or sleep disorders. As the risk for the development of these symptoms is higher upon abrupt discontinuation, gradual reduction of dose is recommended.

Drug Abuse

Lorazepam has abuse potential. Patients with particular risk include those with a history of drug and/ or alcohol abuse.

Drug abuse is a known risk for benzodiazepines, and patients should be monitored accordingly when receiving lorazepam. Benzodiazepines may be subject to diversion. There have been reports of overdose related deaths when benzodiazepines are abused with other CNS depressants including opioids, other benzodiazepines, alcohol and/or illicit substances. These risks should be considered when prescribing or dispensing lorazepam. To reduce these risks the lowest effective dose should be used, and patients should be advised on the proper storage and disposal of unused drug to prevent diversion (e.g. through friends and relatives).

This medicinal product contains lactose.

Each tablet contains 67.65 mg lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Drugs Interactions

If lorazepam tablets are taken together with other central depressants (e.g. barbiturates, analgesics, psychotropic drugs such as antidepressants, sedatives/hypnotics, beta-blockers, anxiolytics, narcotics, sedative antihistamines, anticonvulsants and anesthetics) or with alcohol, a mutual potentiation of central depressant effects including respiratory depression will occur.

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).

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

Concurrent administration of lorazepam with valproate may result in increased plasma concentrations and reduced clearance of lorazepam. Therefore, lorazepam dosage should be reduced by about 50% when given together with valproate.

Concurrent administration of lorazepam with probenecid may result in a more rapid onset of action or prolonged effects as a result of increased half-life and reduced total clearance. Therefore, lorazepam dosage should be reduced by 50% when lorazepam and probenecid are given together.

The additional use of theophylline and aminophylline may reduce the sedative effects of benzodiazepines, such as lorazepam.

Lorazepam has no effect on the activity of the oxidative metabolic system (cytochrome P450 system). Thus, interactions due to enzyme-inducing effects on this system (e.g. with cimetidine) are not to be expected.

4.6 Use in Special Populations

Pregnancy

Lorazepam should not be used during pregnancy.

Several studies have suggested an association between the use of benzodiazepines during the first trimester of pregnancy and an increased risk of congenital malformations.

Samples of human umbilical cord blood have suggested that benzodiazepines and their glucuronide metabolites cross the placenta. The lorazepam glucuronide can be detected in neonatal plasma for up to 7 days after birth. Glucuronidation of lorazepam may competitively impair the conjugation of bilirubin which may favor development of hyperbilirubinemia in the neonate.

Neonates from mothers given benzodiazepines towards the end of their pregnancy may develop dependence and are therefore exposed to the risk of withdrawal symptoms during the postnatal phase.

Symptoms such as hypoactivity, hypotension, hypothermia, apnea, respiratory depression, feeding

problems and impaired adaptation of body temperature to cold ambient temperature have been reported in neonates whose mothers had been given benzodiazepines towards the end of pregnancy or during delivery.

Lactation

Lorazepam has been found in breast milk and should therefore not be given to nursing mothers.

Neonates of mothers taking benzodiazepines and nursing have shown sedation and difficulties in suckling. In such cases, pharmacological effects as well as irritation and sedation of the infant should be observed.

4.7 Effects on Ability to Drive and Use Machines

Lorazepam has major effects on the ability to drive and operate machinery.

Even with use as recommended lorazepam may significantly affect the ability to drive and operate machinery.

This especially holds when used together with alcohol.

Therefore, driving of vehicles, operating of machinery and other dangerous activities should be avoided at least during the first days of treatment. The decision in each individual case must be taken by the treating physician under adequate consideration of the individual reactions and the respective dosage.

4.8 Undesirable Effects

The following definitions for the frequency of adverse drug reactions (with causal relationship) have been used (according to CIOMS):

Very common: ≥1/10
Common: ≥1/100, <1/10
Uncommon: ≥1/1,000, <1/100
Rare: ≥1/10,000, <1/1,000
Very rare: <1/10,000
Not known: Cannot be estimated from the available data

System organ class	Very common	Common	Uncommon	Frequency not known
Blood and lymphatic system disorders				Thrombocytopenia, agranulocytosis, pancytopenia
Immune system disorders				Hypersensitivity reactions, anaphylactic/anaphylactoid reactions
Endocrine disorders				SIADH
Metabolism and nutrition disorders				Hyponatremia

System organ class	Very common	Common	Uncommon	Frequency not known
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, drug abuse, drug dependence
Nervous system disorders*	Sedation, drowsiness	Ataxia, dizziness		Extrapyramidal symptoms, tremor, dysarthria/slurred speech, headache, convulsions/seizures, amnesia, coma, impaired attention/concentration, balance disorder
Eye disorders				Visual disturbances including diplopia and blurred vision
Ear and labyrinth disorders				Vertigo
Vascular disorders				Hypotension, lowering in blood pressure
Respiratory, thoracic and mediastinal disorders				Respiratory depression^{+}, apnea, worsening of sleep apnea, worsening of obstructive pulmonary disease
Gastrointestinal disorders			Nausea	Constipation
Hepatobiliary disorders				Jaundice
Skin and subcutaneous tissue disorders				Angioedema, allergic skin reactions, alopecia
Musculoskeletal and connective tissue disorders		Muscle weakness		
Reproductive system and breast disorders			Impotence	
General disorders and administration site conditions	Fatigue	Asthenia		Hypothermia, drug withdrawal syndrome

System organ class	Very common	Common	Uncommon	Frequency not known
Investigations				Increase in bilirubin, increase in liver transaminases and in alkaline phosphatase

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

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

Reporting of suspected adverse reactions

Reporting of suspected adverse reactions after authorization 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.

4.9 Overdose

Principally, the possibility of multiple intoxication should always be considered, e.g. with the ingestion of multiple drugs for a suicide attempt.

Post-marketing experience shows that lorazepam overdose mostly occurs in combination with alcohol or with other drugs.

Symptoms of intoxication

Overdosage of benzodiazepines is usually manifested by central nervous depression of varying degree from drowsiness to coma. Symptoms of mild overdose may include drowsiness, confusion, somnolence, lethargy, ataxia, paradoxical reaction, dysarthria, myalgia and hypotension. In cases of severe intoxication central respiratory and circulatory depression or unconsciousness may occur (ICU monitoring!). With the combination with other central depressants or alcohol the risk is increased as a result of multiple intoxication and the risk of lethal outcome must be considered.

During the resolution phase of intoxication high-grade excitation states have been observed.

Treatment of intoxications

The usual general supportive and symptomatic measures are recommended; vital functions should be monitored. Induced vomiting is not recommended in the presence of a risk of aspiration. Gastric lavage may be indicated if performed early or in patients with signs of intoxication. Administration of activated charcoal may limit absorption. Assisted ventilation for respiratory insufficiency. Hypotension may be treated with plasma replacement fluid. For the neutralization of the central depressant effect of benzodiazepines the specific benzodiazepine antagonist flumazenil may be useful and may be used in addition to appropriate measures – but not as substitution – in hospitalized patients. Physicians should consider the possibility of seizures in association with flumazenil treatment, especially in long-term lorazepam users and tricyclic antidepressant overdoses.

The value of hemodialysis in intoxication with lorazepam is low, but it may be meaningful in cases where mixed intoxications cannot be excluded. Lorazepam is poorly dialyzable. Lorazepam glucuronide (the inactive breakdown product) is highly dialyzable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of Action

Pharmacotherapeutic group: Psycholeptics, Anxiolytics, benzodiazepine derivatives; ATC code: N05B A06.

Lorazepam is a psychotropic substance from the class of 1,4-benzodiazepines with relaxant, sedative, hypnotic and anxiolytic effects. Moreover, lorazepam shows muscle relaxant and anticonvulsant effects.

5.2 Pharmacodynamic Properties

Lorazepam shows a very high receptor affinity to specific binding sites in the CNS. These benzodiazepine receptors are in close functional connections with the receptors of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). After binding to the benzodiazepine receptor lorazepam increases the inhibitory effect of GABA-ergic transmission.

5.3 Pharmacokinetic Properties

Absorption

Following oral dosing lorazepam is rapidly and almost completely absorbed. With a dose of 2 mg the average absorption half-lives measured vary between 10.8 and 40.4 minutes.

With an oral dose of 2 or 4 mg lorazepam the average C_{max} levels measured after 1 – 2.5 hours range between 16.9 and 27.6 ng/ml and 51.3 und 58 ng/ml, respectively.

Volume of distribution

The volume of distribution is about 1.3 L/kg. Unbound lorazepam crosses the blood-brain barrier by passive diffusion. Lorazepam at concentrations of 160 ng/ml shows approx. 92% protein binding.

Passage into the CNS

The concentrations of lorazepam and conjugates found in the CSF are clearly lower than the simultaneous plasma concentrations (on average less than 5% of the respective plasma levels).

Placenta passage

Lorazepam and lorazepam glucuronide cross the placenta barrier and enter into fetal circulation and amniotic fluid. Neither lorazepam nor the glucuronide show accumulation in the fetus. The neonate also inactivates lorazepam by glucuronidation, but more slowly than the mother.

Passage into breast milk

Lorazepam and the glucuronide are excreted into breast milk in minor amounts. Approximately 13% of the maximum maternal serum concentration for lorazepam and about 20% for the glucuronide were measured.

With a (relatively high) maternal daily dosage of 5 mg this corresponds to a content of about 12 mg lorazepam and 35 mg lorazepam glucuronide per liter breast milk.

Biotransformation

In animal experiments the hardly active glucuronide has been shown as the primary metabolite of lorazepam which is virtually completely biotransformed.

Active metabolites are not being formed. Following IM administration of 4 mg lorazepam the concentration of the glucuronide which is being formed at a half-life of about 3.8 hours can already be measured after a few minutes. The concentration of this metabolite reaches a plateau level after 4 hours which is maintained for about 8 hours.

Elimination

Various studies have described levels of 12 to 16 hours for the elimination half-life. The elimination half-life determined for the glucuronide is 12.9 to 16.2 hours.

With a daily oral dose of 3 mg lorazepam steady-state concentration was reached after 2-3 days. The minimum steady-state concentration was on average 25.3 ng/ml, but very marked interindividual variations were seen (17.1 – 43.8 ng/ml). Comparison of half-life after a single dose and that measured in the washout phase (14.9 h vs. 14.2 h) shows that lorazepam neither inhibits nor induces its breakdown. The accumulation ratio (AUC on Day 8/ AUC on Day 1) was maintained at 1.88. After administration of 2 mg ^{14}C labeled lorazepam 87.8% of the radioactivity was recovered in the 120-hour urine and 6.6% in the feces. Less than 0.5% of the dose are excreted in urine as unchanged lorazepam. The primary metabolite in 120-hour urine is the glucuronide (74.5% of dose).

During the first days of life the elimination half-life may be the 2- to 4-fold of the maternal half-life. With the exception of the first days of life terminal elimination half-life shows no essential age-dependence.

Elderly patients

Elderly patients typically show response to lower benzodiazepine doses than younger patients.

Elimination with impaired renal function

Metabolic inactivation and plasma half-lives of lorazepam are unchanged in the presence of existing renal insufficiency, but elimination of the pharmacodynamically inactive glucuronide is significantly reduced.

With increasing renal impairment and cumulation of lorazepam glucuronide biliary elimination increases.

Dialysability and strategy for forced diuresis, e.g. in intoxication

With impaired renal function clearance of lorazepam is normal, while the pharmacodynamically inactive lorazepam glucuronide shows cumulation. With a 6-hour hemodialysis only 8% of the unconjugated substance could be eliminated, but 40% of the glucuronide. Thus, the value of hemodialysis in the case of major intoxication is not significant. The same also holds for forced diuresis.

Elimination with impaired hepatic function

Absorption and metabolization of lorazepam is not significantly affected by existing hepatic disease (hepatitis, cirrhosis). Obviously, glucuronidation in the presence of hepatic disease is not substantially affected. However, significant hepatic dysfunction may lead to a prolongation of terminal half-life.

Relationship between concentration and effects

Plasma lorazepam level shows a proportional relationship to the dose administered.

There is no evidence suggesting accumulation of oral lorazepam over a period of 6 months.

6. NONCLINICAL PROPERTIES

6.1 Animal Toxicology or Pharmacology

Subchronic and chronic toxicity

In chronic toxicity studies lorazepam was studied in rats (80 weeks) and dogs (12 months) with oral administration. Histopathologic, ophthalmologic and hematologic examinations as well as organ function tests showed virtually no or only few significant, biologically irrelevant changes at high doses.

After treatment for more than one year at doses of 6 mg/kg/day isolated cases of esophageal dilation were observed in rats. These were reversible when treatment was stopped within two months of the first occurrence. The clinical relevance of this finding (more than 50 fold of maximum therapeutic dose) is unknown.

Tumorigenic potential

Oral administration of lorazepam for 18 months in rats and mice revealed no signs of a tumorigenic potential.

Mutagenic potential

A mutagenicity study with lorazepam in *Drosophila melanogaster* showed that lorazepam is devoid of any mutagenic activity.

Reproduction toxicity

In a pre-implantation study in rats given oral doses of 20 mg/kg lorazepam, no impairment of fertility was observed.

The effects of lorazepam on embryonal and fetal development and reproductivity were studied in rabbits, rats and mice. The animals used had been shown to be sensitive to the known teratogens used. In the context of these tests no signs of teratogenic effects or a disturbance of reproductivity could be identified.

The experimental studies produced signs of behavioral disorders of the offspring of dams with long-term exposure to lorazepam.

7. DESCRIPTION

Lorazepam Tablet I.P. 1 mg - White, round, flat, beveled tablets, plain on both sides
Lorazepam Tablet I.P. 2 mg - Light orange flat beveled tablets, plain on both sides

8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

None.

8.2 Shelf-life

Pack presentation	Shelf Life
Ativan Tablets 1 mg / Ativan Tablets 2 mg: 30 tablets are blister packed using one side printed Aluminium foil and amber colour PVC film	24 months
Ativan Tablets 2 mg: 30 tablets are blister packed using one side printed Aluminium foil as lidding foil and Multi Layered Cold–Formable Blister Film with composition of nylon/ Aluminium/ PVC as base foil.	12 months

8.3 Packaging Information

Ativan Tablets 1 mg / Ativan Tablets 2 mg:
30 tablets are blister packed using one side printed Aluminium foil and amber colour PVC film.

Ativan Tablets 2 mg:
30 tablets are blister packed using one side printed Aluminium foil as lidding foil and Multi Layered Cold–Formable Blister Film with composition of nylon/ Aluminium/ PVC as base foil.

8.4 Storage and Handling Instructions

Store below 30°C. Protect from light and moisture.

Instructions for Use and Handling

Keep out of reach of children.

9. PATIENT COUNSELLING INFORMATION

The use of benzodiazepines may unmask suicidal tendency in depressed patients and should not be used without adequate antidepressant therapy. Patients on Lorazepam should be followed closely for signs and symptoms of respiratory depression and sedation. Lorazepam should be used with caution in patients with impaired respiratory function. Patients should be advised that tolerability of other tranquilizers may be reduced and these should either be discontinued or given at lower dosage when using lorazepam. 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.

Benzodiazepines may trigger anterograde amnesia mostly occurring few hours after administration Lorazepam should be used with caution in patients with hepatic insufficiency and/or encephalopathy.

The use of benzodiazepines, including lorazepam, may lead to physical and psychological dependence Withdrawal symptoms, in particular severe symptoms, are seen at higher frequency in those patients given high doses for prolonged periods. Patients should be instructed to consult their doctor before either reducing the dose or abruptly discontinuing the drug by themselves. Lorazepam should be used with caution in patients with paragroup allergy. Patients who develop angioedema after treatment with a benzodiazepine should not be rechallenged with the drug. In patients with severe hepatic dysfunction use of lorazepam is contraindicated.

10. DETAILS OF MANUFACTURER

Manufactured by:
Pfizer Limited, Plot No. L-137, Phase III A, Verna Industrial Estate, Verna, Salcete - Goa

11. DETAILS OF PERMISSION OR LICENSE NUMBER WITH DATE

Manufacturing Licence No*.: 544 dated 01 Dec 2014 (*The manufacturing license is renewed every 5 years as per Indian regulations).

12. DATE OF REVISION

March 2024