Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ativan 4 mg/ml Solution for

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule contains 4 mg/ml lorazepam (4 mg per 1 ml ampoule).

Excipient(s) with known effect:
Each ml contains 0.02 ml benzyl alcohol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection (injection).
A clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Premedication for dental or general surgery or for minor invasive investigations, e.g. bronchoscopy, arteriography, endoscopy.

The treatment of acute anxiety states, acute excitement or acute mania.

The control of status epilepticus.

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 in all patients (see section 4.4).

Method of administration:

Ativan Injection can be given intravenously or intramuscularly. However, the intravenous route is to be preferred. Care should be taken to avoid injection into small veins and intra-arterial injection.

Absorption from the injection site is considerably slower if the intramuscular route is used and as rapid an effect may be obtained by oral administration of Ativan tablets.

Ativan should not be used for long-term chronic treatment.

Preparation of the injection

Intramuscular administration:

A 1:1 dilution of Ativan Injection with normal saline or Sterile Water for Injection BP is recommended in order to facilitate intramuscular administration.

Intravenous administration:

For intravenous administration, Ativan Injection should always be diluted with saline or Sterile Water for Injection BP as a 1:1 dilution.

Ativan Injection is presented as a 1ml solution in a 2ml ampoule to facilitate dilution.

Ativan Injection should not be mixed with other drugs in the same syringe.

Dosage:

Premedication:
Adults: 0.05 mg/kg (3.5 mg for an average 70 kg man). By the intravenous route the injection should be given 30-45 minutes before surgery when sedation will be evident after 5-10 minutes and maximal loss of recall will occur after 30-45 minutes.

By the intramuscular route the injection should be given 1-$1^1/_2$ hours before surgery when sedation will be evident after 30-45 minutes and maximal loss of recall will occur after 60-90 minutes.

Paediatric population: Ativan Injection is not recommended in children under 12 years.

Acute Anxiety:
Adults: 0.025-0.03 mg/kg (1.75-2.1 mg for an average 70 kg man). Repeat 6 hourly.

Paediatric population: Ativan Injection is not recommended in children under 12 years.

Status epilepticus:
Adults: 4 mg intravenously

Paediatric population: 2 mg intravenously

Elderly and debilitated patients: Elderly and debilitated patients may respond to lower doses and half the normal adult dose may be sufficient.

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

Elderly and debilitated patients
For elderly and debilitated patients reduce the initial dose by approximately 50% and adjust the dosage as needed and tolerated (see section 4.4 Special warnings and precautions for use)

4.3 Contraindications

1. Hypersensitivity to benzodiazepines, including lorazepam or to any of the excipients (propylene glycol, polyethylene glycol and benzyl alcohol) listed in section 6.1.

2. Ativan Injection should not be used in patients with severe hepatic or pulmonary insufficiency.

3. Myasthenia gravis

4. Sleep apnoea syndrome

5. Ativan Injection is not recommended for out-patient use unless the patient is accompanied.

4.4 Special warnings and precautions for use

Prior to use, Ativan Injection may be diluted for IM administration and should always be diluted for IV administration with equal amounts of compatible diluent (see section 4.2). Intravenous injection should be administered slowly except in the control of status epilepticus where rapid injection is required.

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 re-challenged with the drug.

Patients should remain under observation for at least eight hours and preferably overnight. When Ativan Injection is used for short procedures on an outpatient basis, the patient should be accompanied when discharged.

Patients should be advised that their tolerance for alcohol and other CNS depressants will be diminished in the presence of Ativan Injection.Alcoholic beverages should not be consumed for at least 24 to 48 hours after receiving Ativan Injection.

Extreme care must be taken in administering Ativan Injection to elderly or very ill patients and to those with limited pulmonary reserve or compromised respiratory function (e.g. chronic obstructive pulmonary disease [COPD]), because of the possibility that apnoea and/or cardiac arrest may occur. Care should be taken when administering Ativan Injection to a patient with status epilepticus, especially when the patient has received other central nervous system depressants.

Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Limit dosages and durations to the minimum required.

There is no evidence to support the use of Ativan Injection in coma or shock.

Ativan 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. The use of benzodiazepines in these patients should not be used without adequate antidepressant therapy.

Pre-existing depression may emerge during benzodiazepine use.

There are no clinical data available for Ativan Injection with regard to abuse or dependence. However, based upon experience with oral benzodiazepines, doctors should be aware that repeated doses of Ativan Injection over a prolonged period of time may lead to physical and psychological dependence. In normal acute usage dependence is unlikely to occur but the risk increases with higher doses and longer-term use and is further increased in patients with a history of alcoholism, drug abuse or in patients with marked personality disorders. Therefore use in individuals with a history of alcoholism or drug abuse should be avoided.

In general, benzodiazepines should be prescribed for short periods only (e.g. 2-4 weeks). Continuous long-term use of lorazepam is not recommended.

Dependence may lead to withdrawal symptoms, especially if treatment is discontinued abruptly. Therefore, the drug should be discontinued gradually – using the oral preparation if necessary.

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

Withdrawal symptoms (e.g. rebound insomnia) can appear following cessation of recommended doses after as little as one week of therapy. Abrupt discontinuation of lorazepam should be avoided and a gradual dosage-tapering schedule followed after extended therapy.

Abrupt termination of treatment may be accompanied by withdrawal symptoms. Symptoms reported following discontinuation of oral benzodiazepines include anxiety, depression, headache, insomnia, tension, muscle pain, restlessness, confusion, irritability, 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: dysphoria, dizziness, derealisation, depersonalisation, hyperacusis, persistent tinnitus, numbness and tingling of the extremities, hypersensitivity to light, noise, and physical contact/perceptual changes, involuntary movements, nausea, vomiting, diarrhoea, loss of appetite, hallucinations/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 antidepressants.

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.

Lorazepam may have abuse potential especially in patients with a history of drug and/or alcohol abuse.

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

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.

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.

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.

Paradoxical reactions such as restlessness, agitation, irritability, aggressiveness, delusion, rage, nightmares, hallucinations, psychoses, and inappropriate behaviour 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.

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.

Ativan Injection contains the excipients polyethylene glycol and propylene glycol. There have been reports of propylene glycol toxicity (e.g. lactic acidosis, hyperosmolality, hypotension) and polyethylene glycol toxicity (e.g. acute tubular necrosis) during administration of lorazepam injection, including at higher than recommended doses. Central nervous system toxicity, including seizures, as well as unresponsiveness, tachypnoea, tachycardia and diaphoresis have also been associated with propylene glycol toxicity. Those prone to propylene glycol accumulation and its potential adverse effects include patients with impaired alcohol and aldehyde dehydrogenase enzyme systems, including children less than 4 years of age; pregnant women; those with severe renal or hepatic disease; and those treated with disulfiram or metronidazole. (see section 4.2)

Intravenous administration of the preservative benzyl alcohol has been associated with serious adverse events, and death in paediatric patients including neonates characterized by central nervous system depression, metabolic acidosis, gasping respirations, cardio-vascular failure and haematological anomalies ("gasping syndrome"). Although normal therapeutic doses of this product ordinarily deliver amounts of benzyl alcohol that are substantially lower than those reported in association with the "gasping syndrome", the minimum amount of benzyl alcohol at which toxicity may occur is not known. Use only if it is

necessary and if there are no alternatives possible. If given in high volumes, should be used with caution and preferably for short term treatment in subjects with liver or kidney impairment because of the risk of accumulation and toxicity (metabolic acidosis).

Premature and low-birth weight infants may be more likely to develop toxicity.

Benzyl Alcohol containing products should not be used in pre-term or full-term neonates unless strictly necessary.

Elderly patients
Lorazepam should be used with caution in elderly due to the risk of sedation and/or musculoskeletal weakness that can increase the risk of falls, with serious consequences in this population. Elderly patients should be given a reduced dose (see section 4.2 Posology).

4.5 Interaction with other medicinal products and other forms of interactions

Not recommended: Concomitant intake with alcohol

The sedative effects may be enhanced when the product is used in combination with alcohol. This effects the ability to drive and or use machines.

The benzodiazepines, including Ativan Injection produce additive CNS depressant effects including respiratory depression, when co-administered with other medications which themselves produce CNS depression e.g., opioids, barbiturates, antipsychotics, sedatives/hypnotics, anxiolytics, antidepressants, narcotic analgesics, sedative antihistamines, anticonvulsants, and anaesthetics (see section 4.4).

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.

The addition of scopolamine to Ativan Injection is not recommended, since their combination has been observed to cause an increased incidence of sedation, hallucination and irrational behaviour.

There have been reports of apnoea, coma, bradycardia, cardiac arrest and death with the concomitant use of lorazepam injection solution and haloperidol.

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.

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.

Use of Ativan Injection during the late phase of pregnancy may require ventilation of the infant at birth.

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 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 are insufficient data regarding obstetrical safety of parenteral Ativan, including use in Caesarean section. Such use, therefore, is not recommended.

Benzyl alcohol can cross the placenta, see section 4.4.

Breast-feeding:
There is evidence that lorazepam is excreted, albeit in pharmacologically insignificant amounts, in human breast milk. Therefore, Ativan 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 use machines. Therefore, patients should not drive or operate machinery within 24-48 hours of administration of Ativan Injection and should be advised not to take alcohol (See section 4.5).

4.8 Undesirable effects

Lorazepam is well tolerated and imbalance or ataxia are signs of excessive dosage. 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.

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
Nervous system disorders ±	Sedation, drowsiness	Ataxia, dizziness		Extrapyramidal symptoms, tremor, dysarthria/slurred speech, headache, convulsions/seizures, amnesia, coma,

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)
				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, [β]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
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 dosedependent, with more severe depression occurring with high doses.

Pre-existing depression may emerge during benzodiazepine use.

Tolerance at the injection site is generally good although, rarely pain and redness have been reported after Ativan Injection.

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).

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

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.

Rarely, propylene glycol toxicity and polyethylene glycol toxicity have been reported following higher than recommended doses of Ativan Injection *(See section 4.4)*.

Treatment of overdosage is mainly supportive including monitoring of vital signs and close observation of the patients. An adequate airway should be maintained and assisted respiration used as needed. Hypotension, though unlikely, may be controlled with noradrenaline. Lorazepam is poorly dialyzable. Lorazepam glucuronide, the inactive metabolite, may be highly dialysable.

The benzodiazepine antagonist, flumazenil, may be useful in hospitalised patients for the management of benzodiazepine overdosage. Flumazenil product information should be consulted prior to use. The physician should be aware of a risk of seizure in association with flumenazil treatment, particularly in long-term benzodiazepine users and in cyclic antidepressant overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: benzodiazepine derivatives, ATC code: N05BA06

Ativan is a shorter acting benzodiazepine with anxiolytic, sedative, hypnotic, muscle relaxant and anticonvulsant properties.

5.2 Pharmacokinetic properties

Absorption:
Ativan Injection is readily absorbed when given intramuscularly. Peak plasma concentrations occur approximately 60-90 minutes following intramuscular administration.

Metabolism:
Ativan is metabolised by a simple one-step process to a pharmacologically inactive glucuronide. There is minimal risk of accumulation after repeated doses, giving a wide margin of safety.

There are no major active metabolites.

Elimination:
The elimination half-life is about 12-16 hours when given intramuscularly or intravenously.

5.3 Preclinical safety data

Not Applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzyl alcohol
Propylene glycol
Polyethylene glycol 400

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products other than those mentioned in *section 4.2*.

6.3 Shelf life

Unopened: 15 months
After Opening: Use immediately after opening
After dilution: Use immediately after dilution.

6.4 Special precautions for storage

Store in a refrigerator between 2ºC and 8ºC.

Keep in the outer carton to protect from light.

6.5 Nature and contents of container

1ml solution in 2ml ampoules (Type I glass) with a one-point-cut opening, position marked by red spot in pack sizes of 10.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Ativan Injection should not be mixed with other drugs in the same syringe.
Do not use if solution has developed a colour or precipitate (see section 4.2).

No special requirements for disposal.

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

7 MARKETING AUTHORISATION HOLDER

Pfizer Healthcare Ireland
9 Riverwalk
National Digital Park
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0822/090/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 June 1977

Date of last renewal: 01 April 2007

10 DATE OF REVISION OF THE TEXT

March 2019