Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Lorazepam 2.5 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2.5 mg lorazepam.

Excipient with known effect:
Each tablet contains 172.05 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet
white, round, flat, bevelled, scored, tablets, diameter between 9.0 mm – 9.2 mm, thickness between 3.3 mm – 3.5 mm, and a theoretical weight of 266.3 mg.

The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

FOR SHORT TERM (2-4 weeks only) USE (adults only)
- Symptomatic relief of anxiety that is severe, disabling or subjecting the individual to unacceptable distress occurring alone or in association with insomnia or short-term psychometric, organic or psychotic illness.

AS PREMEDICATION (adults and children 6 years and above)

Before operative dentistry and general surgery

NOT FOR USE
• Long term (i.e. longer than 4 weeks)
• For mild/moderate anxiety
• For insomnia or anxiety in children

4.2 Posology and method of administration

Treatment to be given:
• Under close medical supervision
• At the lowest effective dose
• For the shortest possible duration (not exceeding 4 weeks)

Doses should be individualised
Extension of use should not take place without further clinical evaluation
Chronic use not recommended (little is known of the long term safety and efficacy; potential for dependence–see section 4.4).

When treatment is started the patient should be informed that
• treatment will be of limited duration

• the dosage will be progressively decreased
• there is a possibility of rebound phenomena

Dosage:
Adults:
Anxiety: 1-4mg daily in divided doses.
Insomnia: 1-2mg before retiring

Premedication before operative dentistry or general surgery:
2-3mg the night before operation 2-4mg one to two hours before the procedure

Elderly:
The elderly may respond to lower doses (half normal adult dose or less)
Children (aged 5-13 years):
Premedication: 0.5-2.5mg at 0.05mg/kg to the nearest 0.5mg according to weight, not less than one hour before operation.

Patients with Renal or hepatic impairment:
Lower doses may be sufficient in these patients (See section 4.4). Use in patients with severe hepatic insufficiency is contraindicated. (See section 4.6).

Method of administration
For oral use.

4.3 Contraindications

• Hypersensitivity to benzodiazepines, or to any of the other ingredients.
• Myasthenia gravis.
• Acute pulmonary insufficiency: respiratory depression; sleep apnoea (risk of further respiratory depression).
• Obsessional states (inadequate evidence of safety and efficacy).
• Severe hepatic insufficiency (may precipitate encephalopathy).
• Planning a pregnancy (see section 4.6).
• Pregnancy (unless there are compelling reasons - see section 4.6).
• Benzodiazepines should not be used alone in depression or anxiety with depression (may precipitate suicide).

4.4 Special warnings and precautions for use

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. Due to the potential adverse reactions including ataxia, muscle weakness, dizziness, drowsiness and fatigue (see Section 4.8), Benzodiazepines may be associated with an increased risk of falling especially in elderly patients. As a result, caution should be exercised particularly when getting up at night. The elderly should receive a reduced dose (see section 4.2).

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.

Pre-existing depression may emerge during benzodiazepine use.

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. (see 4.8 Undesirable effects). Therefore, the drug should always be discontinued gradually.

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.

Abuse of benzodiazepines has been reported.

Some loss of efficacy to the hypnotic effect of short-acting benzodiazepines may develop after repeated use for a few weeks. 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 a more specific treatment.

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

Patients with impaired renal or hepatic function 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 haematology 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 Lorazepam 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).

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 (see Undesirable effects).

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.

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 (see also general dose 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).

Contains lactose. Patients with rare hereditary problems of galactose intolerance, the total lactase deficiency or glucose – galactose malabsorption should not take this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Not Recommended:

Alcohol:
Lorazepam should not be used together with alcohol (enhanced sedative effects; impaired ability to drive/operate machinery)

Sodium oxybate
Avoid concomitant use (enhanced effects of sodium oxybate)

HIV-protease inhibitors
Avoid concomitant use (increased risk of prolonged sedation – see below for zidovudine

Take into account:

Opioids
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).

Centrally acting drugs
Enhancement of the central depressive effect may occur if lorazepam is combined with drugs such as neuroleptics, antipsychotics, tranquillisers, antidepressants, hypnotics, analgesics, anaesthetics, barbiturates and sedative antihistamines. The elderly may require special supervision.

Anti-epileptic drugs
Pharmacokinetic studies on potential interactions between benzodiazepines and antiepileptic drugs have produced conflicting results. Both depression and elevation of drug levels, as well as no change have been reported.
Phenobarbital taken concomitantly may result in an additive CNS effect. Special care should be taken in adjusting the dose in the initial stages of treatment.
Side effects may be more evident with hydantoins or barbiturates

Valproate may inhibit the glucuronidation of lorazepam (increased serum levels: increased risk of drowsiness)

Narcotic analgesics
Enhancement of the euphoria may lead to increased psychological dependence

Clozapine
Reports of marked sedation, excessive salivation, hypotension, ataxia, delirium and respiratory arrest when given concurrently with lorazepam.

Muscle relaxants
When taken with muscle relaxants, the overall muscle-relaxing effect may be increased (accumulative) therefore caution is advised, especially in elderly patients and at higher doses (risk of falling, see Section 4.4).

Other drugs enhancing the sedative effect of diazepam
Cisapride, lofexidine, nabilone, disulfiram and the muscle relaxants – baclofen and tizanidine

Compounds that affect hepatic enzymes (particularly cyctochrome P450)
- *Inhibitors* (e.g. cimetidine, isoniazid; erythyromycin; omeprazole; esomeprazole) reduce clearance and may potentiate the action of benzodiazepines. Itraconazole, ketoconazole and to a lesser extent fluconazole and voriconazole are potent inhibitors of the cytochrome P450 isoenzyme CYP3A4 and may increase plasma levels of benzodiazapines. The effects of benzodiazapines may be increased and prolonged by concomitant use. A dose reduction of the benzodiazepine may be required.
- Inducers (e.g. rifampicin) may increase clearance of benzodiazepines

Antihypertensives, vasodilators and diuretics: Enhanced hypotensive effect with ACE-inhibitors, alpha-blockers, angiotensin-II receptor antagonists, calcium channel blockers, adrenergic neurone blockers, beta-blockers, moxonidine, nitrates, hydralazine, minoxidil, sodium nitroprusside and diuretics

Enhanced sedative effect with alpha-blockers or moxonidine.

Dopaminergics
Possible antagonism of the effect of levodopa

Antacids
Concurrent use may delay absorption of lorazepam

Zidovudine
Increased zidovudine clearance by lorazepam

Oestrogen-containing contraceptives
Possible inhibition of hepatic metabolism of lorazepam

Theophylline/aminophylline
Increases metabolism of lorazepam which possibly reduces the effect

Caffeine
Concurrent use may result in reduced sedative and anxiolytic effects of lorazepam.

Grapefruit juice
Inhibition of CYP3A4 may increase the plasma concentration of lorazepam (possible increased sedation and amnesia). This interaction may be of little significance in healthy individuals, but it is not clear if other factors such as old age or liver cirrhosis increase the risk of adverse events with concurrent use.

4.6 Fertility, pregnancy and lactation

Benzodiazepines should not be used during pregnancy, especially during the first and last trimesters. Benzodiazepines may cause foetal damage when administered to pregnant women.

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.

There is a possibility that infants born to mothers who take benzodiazepines chronically during the later stages of pregnancy may develop physical dependence. 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: Lorazepam is excreted in small amounts in breast milk. Mothers who are breast-feeding should not take benzodiazepines. Sedation and inability to suckle have occurred in neonates of lactating mothers taking benzodiazepines.

4.7 Effects on ability to drive and use machines

Patients should be advised that sedation, amnesia, impaired concentration, dizzinesss, blurred vision and impaired muscular function may occur and that, if affected, they should not drive or use machines, or take part in other activities where this would put themselves or others at risk. If insufficient sleep duration occurs, the likelihood of impaired alertness may be increased. Concurrent medication may increase these effects (see section 4.5).

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you

- It is an offence to drive while under the influence of this medicine

However, you would not be committing an offence (called 'statutory defence') if:
- The medicine has been prescribed to treat a medicinal or dental problem and
- You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
- It was not affecting your ability to drive safely''

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.
Most frequently reported adverse reactions associated with benzodiazepines include daytime drowsiness, dizziness, muscle weakness, and ataxia.

Adverse reactions are listed by frequency:

Very common:	≥ 1 / 10	Rare:	≥ 1 / 10,000 to < 1 / 1,000
Common:	≥ 1 / 100 to < 1 /10	Very rare:	< 1 / 10,000
Uncommon:	≥ 1 / 1,000 to < 1 / 100	not known:	(cannot be estimated from the available data)

Blood and lymphatic system disorders
Very rare: thrombocytopenia, leucopenia, agranulocytosis, , pancytopenia,

Immune system disorders
Very rare: hypersensitivity including anaphylaxis / anaphylactoid reactions

Endocrine disorders
Very rare: Inappropriate antidiuretic hormone secretion, hyponatramia

Psychiatric disorders
Rare: Confusion, depression and unmasking of depression,
numbed emotions, disinhibition, euphoria, appetite changes, sleep disturbance, change in libido, decreased orgasm.
Unknown: Dependence, Suicidal ideation/attempt
Paradoxical reactions such as restlessness, agitation, irritability, aggressiveness, delusion, rage, insomnia, nightmares, hallucinations, psychoses, sexual arousal, and inappropriate behaviour have been occasionally reported during use.

Nervous system disorders:
Very common: Daytime drowsiness, sedation /
Common:Dizziness, ataxia
Rare: headache, reduced alertness, dysarthria/slurred speech, transient anterograde amnesia or memory impairment
Very rare: Tremor, extrapyramidal reactions, Coma (see 4.9 Overdose)

Eye disorders:
Rare: visual disturbances (diplopia, blurred vision)

Vascular disorders:
Rare: Hypotension (see 4.4 Special warnings and precautions)

Respiratory, thoracic and mediastinal disorders:
Rare: Apnoea, worsening of sleep apnoea, worsening of obstructive pulmonary disease. Respiratory depression (see 4.9 Overdose).

Gastrointestinal disorders:
Rare: Nausea, constipation, salivation changes

Hepatobiliary disorders:

Rare:Abnormal liver function test values (increase in bilirubin, transaminases, alkaline phosphatase), jaundice

Skin and subcutaneous tissue disorders:
Rare: Rash, allergic dermatitis

Musculoskeletal disorders:
Common: Muscle weakness,

Reproductive system and breast disorders:

Rare: Impotence

General disorders
Common: Asthenia, fatigue

Very rare: Hypothermia

Drug withdrawal symptoms (see 4.4 Special warnings and precautions)

Symptoms reported following discontinuation of benzodiazepines include headaches, muscle pain, anxiety, tension, depression, insomnia, 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: derealisation; depersonalisation; hyperacusis; tinnitus; numbness and tingling of the extremities; hypersensitivity to light, noise, and physical contact; involuntary movements; hyperreflexia, tremor, nausea, vomiting; diarrhoea, abdominal cramps, loss of appetite, agitation, palpitations, tachycardia, panic attacks, vertigo, short-term memory loss hallucinations/delirium; catatonia; hyperthermia, convulsions. Convulsions 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.

Injury, poisoning and procedural complications
Not known: Fall

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 overdose with any drug, it should be borne in mind that multiple agents may have been taken.

Overdose 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 ataxia, hypotension, respiratory depression, coma, and very rarely death.

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.

The benzodiazepine antagonist, flumazenil, may be useful in hospitalised patients for the management of benzodiazepine overdose. Flumazenil product information should be consulted prior to use.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Lorazepam is a benzodiazepine drug with anxiolytic, sedative and hypnotic 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.

5.3 Preclinical safety data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Povidone (K 30)
Crospovidone, Type A
Maize starch
Microcrystalline cellulose, E 460
Sodium starch glycollate
Polacrilin potassium
Magnesium stearate, E 572

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

PVC / PE / PVDC – Aluminium blister: 15 months
oPA / ALU / PVC – Aluminium blister: 24 months

6.4 Special precautions for storage

Store below 25^{o}C. Store in original packaging to protect from light.

6.5 Nature and contents of container

Blisters of opaque PVC / PE / PVDC – Aluminium or oPA / ALU / PVC – Aluminium.

Packs containing: 10, 14, 15, 20, 28, 30, 50, 60, 90, 100 and (hospital/pharmacy only) 500 tablets are available.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements. Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Aspire Pharma (Malta) LimitedTrident Park, Notabile Gardens No. 2, Level 3, Mdina Road, Central Business District Birkirkara CBD2010, Malta

8 MARKETING AUTHORISATION NUMBER

PA23142/007/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18th December 2012
Date of last renewal: 22nd September 2017

10 DATE OF REVISION OF THE TEXT

April 2024