SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Lorazepam Tablets 1mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Lorazepam 1mg

Excipient(s) with known effect:
Lactose 80mg
For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Uncoated tablets

Pale blue, oblong shaped tablet, size 8mm x 3.5mm with embossed ‘L/1’ on one face and ‘PV’ on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications:

Lorazepam tablets are recommended for short term use of approximately 2-4 weeks for adults only, as long term use may lead to dependence and withdrawal symptoms

Lorazepam is indicated for:

- Short-term symptomatic treatment of anxiety and insomnia caused by anxiety, where the anxiety is severe, disabling or subjecting the individual to extreme distress along with psychometric, organic or psychotic illness.
- Premedication before general anaesthesia or before minor surgical procedures, investigations or operative dentistry.

4.2 Posology and method of administration

General:

For oral administration.

The dosage and duration of therapy should be individualised. The lowest effective dose should be prescribed for the shortest time possible. Since the risk of withdrawal and rebound phenomena is greater after abrupt withdrawal, the drug should be discontinued gradually for all patients (see section 4.4).
The maximum daily dose of 4mg should not be exceeded.
In general the duration of treatment varies from a few days to 4 weeks, including the tapering off process.
Extension of the treatment period should not take place without re-evaluation of the need for continued therapy.
If the daily dose is taken as single dose in the evening it should not be taken on a full stomach. Due to a delayed onset of effect and depending on the length of the sleeping period a hang-over effect might be possible during the following day (see Section 4.4).

Adults:
Anxiety: 1-4mg daily in divided doses.
Insomnia caused by anxiety: Initial dose of 1mg before retiring to sleep. Usual Dose 1-2mg before retiring to sleep.
Premedication: 2-3mg the night before operation; 2-4mg one to two hours before Operation

Dentistry:
1-2.5mg, 1 ½-2 hours before dental treatment. Premedication before operative dentistry or surgery: 2mg – 4mg, one to two hours prior to the operation

Children and adolescents:
Lorazepam should not be used in children and adolescents under 18 years of age, as safety and efficacy have not been established in this population, except as indicated below.

Premedication: before operative dentistry or surgery
Children aged 5-12 years.0.05-0.1mg/kg (max. 4mg) at least one hour before procedure.

Aged 12 – 18 years and Adults: Premedication before operative dentistry or surgery: 1–4 mg at least one hour before procedure.

Same dose may be given the night before procedure in addition to, or to replace dose before procedure.

Not recommended for use in children under 5 years of age.

Elderly and debilitated patients:
The elderly and debilitated patients may respond to lower doses and half the normal adult dose or less may be adequate. The starting dose should be half of the recommended adult dose. This initial dose should be adjusted according to clinical response and tolerance.

Hepatic impairment:

Use in patients with severe hepatic impairment is contraindicated (see section 4.3).
In patients with moderate to mild hepatic impairment, lower doses may be adequate. The starting dose should be half the recommended adult dose. Such patients should be carefully monitored for clinical response and tolerability, and dosage adjusted accordingly (see section 4.4).

Renal impairment:
In patients with severe to mild renal impairment, lower doses may beadequate. The starting dose should be half the recommended adult dose. Such patients should be carefully monitored for clinical response and tolerability, and dosage adjusted accordingly (see section 4.4).

Prior to starting treatment with Lorazepam, a discussion should be held with patients to put in place a strategy for ending treatment with Lorazepam in order to minimise the risk of dependence, addiction and drug withdrawal syndrome (see section 4.4).

Treatment should be given for the shortest possible duration. If this medicine is being used for the treatment of epilepsy this medicine should be used for as long as the prescriber considers it necessary.

4.3 Contraindications

- Hypersensitivity to lorazepam, or to other benzodiazepines or to any of the excipients (see section 6.1).
- Acute pulmonary insufficiency, Respiratory depression, Chronic psychosis, phobic or obsessional states.
- Myasthenia gravis, sleep apnoea syndrome, severe hepatic insufficiency and acute porphyria.
- Planning a pregnancy (see section 4.6)
- A history of persistent drug and/or alcohol abuse (see also Section 4.4)

4.4 Special warnings and precautions for use:

- 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.

- 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, which may be fatal. Patients who develop Angioedema following treatment with a benzodiazepine should not be rechallenged.

Abuse of benzodiazepines has been reported, particularly in patients with a history of drug and / or alcohol abuse.

- Patients should be advised that since their tolerance for alcohol and other CNS depressants will be diminished in the presence of lorazepam, CNS depressants should either be avoided or taken in reduced dosage and alcohol should be avoided.
- 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, it is necessary to take suitable precautions and to prescribe appropriate amounts as large quantities of Lorazepam should not be prescribed to these patients.
- Benzodiazepines should be used with extreme caution in patients with a history of alcohol or drug abuse. (See section 4.3)

Duration of treatment:

The duration of treatment should be as short as possible (see section 4.2) depending on the indication, generally it varies from a few days up to 4 weeks, including the tapering off process. Extension beyond these periods should not take place without re – evaluation of the situation.

It may be useful to inform the patient when treatment is started that it will be of limited duration and to explain precisely how the dosage will be progressively decreased. Moreover it is important that the patient should be aware of the possibility of rebound phenomena, thereby minimising anxiety over such symptoms should they occur while the medicinal product is being discontinued.

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.

Dependence:

- Pre-existing depression may emerge during benzodiazepine use. The use of benzodiazepines may lead to physical and psychological dependence upon these products. The risk of dependence 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. Withdrawal symptoms may consist of headaches, muscle pain, extreme anxiety, sleep disorders, tension, restlessness, confusion and irritability. In severe cases the following symptoms may occur: derealisation, depersonalisation, Hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures. Seizures may be more common in patients with pre –existing seizure disorders, or who are taking other drugs that lower the seizure threshold such as antidepressants.
  The patient should also be made aware of the possibility of "rebound" phenomena to whereby the symptoms that led to treatment with a benzodiazepine recur in an enhanced form may occur on withdrawal of treatment. It may be accompanied by other reactions including mood changes, anxiety or sleep disturbances and restlessness. Since the risk of withdrawal phenomena / rebound phenomena is greater after abrupt discontinuation of treatment, it is recommended that the dosage is decreased gradually.
  After abrupt termination of treatment withdrawal symptoms can occur even after several days of treatment and at therapeutic doses.

Tolerance:

- Some loss of efficacy to the hypnotic effects of short-acting benzodiazepines may develop after repeated use for a few weeks. There is evidence that tolerance developsto the sedative effects of benzodiazepines.
- Lorazepam may have abuse potential, especially in patients with a history of alcohol and / or drug abuse.

Specific patients groups:

- Benzodiazepines should not be given to children without careful assessment of the need to do so; the duration of treatment must be kept to a minimum.
- 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 haematological and liver-function assessments are recommended where repeated courses of treatment are considered clinically necessary.
- Caution should be used in the treatment of patients with acute narrow-angle glaucoma.

Amnesia:

- 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).

Psychiatric and paradoxical reactions:

- Psychiatric and Paradoxical reactions like restlessness, agitation, irritability, aggressiveness, delusion,rages, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects are known to occur when using benzodiazepines 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.

Elderly patients should be warned of the risk of falls due to the myelo relaxant effect of lorazepam.

Caution should be used in patients with ataxia and acute intoxication with alcohol or other CNS active agents.

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

<u>Drug dependence, tolerance and potential for abuse</u>

Drug addiction comprises behavioural, cognitive and physiological phenomena that may include a strong desire to take the drug, difficulties in

controlling drug use and possible tolerance or physical dependence. Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, which manifests as withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug. Addiction and dependence are related but distinct presentations and in discussing these themes, terminology that apportion blame to the individual should be avoided.

For all patients, prolonged use of this product may lead to drug dependence and addiction but can occur with short-term use at recommended therapeutic doses. The risks are increased in individuals with current or past history of substance misuse disorder (including alcohol misuse) or mental health disorder (e.g., major depression).

Additional support and monitoring may be necessary when prescribing for patients at risk of drug misuse.

A comprehensive patient history should be taken to document concomitant medications, including over-the-counter medicines and medicines obtained on-line, and past and present medical and psychiatric conditions.

Patients may find that treatment is less effective with chronic use and express a need to increase the dose to obtain the same level of symptom control as initially experienced. Patients may also supplement their treatment with additional medications to achieve the same effect. These could be signs that the patient is developing tolerance. The risks of developing tolerance should be explained to the patient.

Overuse or misuse may result in overdose and/or death. It is important that patients only use medicines that are prescribed for them at the dose they have been prescribed and do not give this medicine to anyone else.

Patients should be closely monitored for signs of misuse, abuse, or addiction.

The clinical need for treatment with Lorazepam should be reviewed regularly, with frequent assessments of patients being undertaken during the course of their treatment.

Drug withdrawal syndrome

Prior to starting treatment with Lorazepam, a discussion should be held with patients to explain the risk of dependence, addiction, and drug withdrawal syndrome. A withdrawal strategy for ending treatment with Lorazepam should also be put in place with the patient before starting treatment (there

may be exceptions to this in specific clinical situations such as symptom management in end of life palliative care, and for use in epilepsy).

Drug withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. When a patient no longer requires therapy, it is advisable to taper the dose gradually to minimise symptoms of withdrawal. Tapering from a high dose may take in excess of weeks or months. Patients should be informed of this when the medication is first prescribed.

The reduction schedule for a patient should be tailored to the individual and should be modified to allow intolerable withdrawal symptoms to improve before making the next reduction. If using a published withdrawal schedule, apply it flexibly to accommodate the person's preferences, changes to their circumstances and the response to dose reductions.

Benzodiazepines: Suggest a slow stepwise rate of reduction proportionate to the existing dose, so that decrements become smaller as the dose is lowered, unless clinical risk is such that rapid withdrawal is needed.

If a patient develops withdrawal reactions, consider pausing the taper or increasing the dosage to the previous tapered dosage level.

If women take this drug during pregnancy, there is a risk that their newborn infants will experience neonatal withdrawal syndrome.

4.5 Interaction with other medicinal products and other forms of interaction

Not Recommended:

- Alcohol Concomitant alcohol intake should be avoided. (The sedative effects of lorazepam may be enhanced when the product is used in combination with alcohol. This affects the ability to drive/operate machinery).

Take into account:

- Sodium oxybate (enhanced effect).
- HIV protease inhibitors like zidovudine (increased risk of prolonged sedation. Increased zidovudine clearance by lorazepam).
- CNS depressants: benzodiazepines, including lorazepam, produce additive
- CNS depressant effects when co – administered with other drug products that produce CNS depression, e.g.neuroleptics, antipsychotics, tranquillisers, antidepressants, hypnotics, narcotic analgesics, anaesthetics, anxiolytics barbiturates and sedative antihistamines, anticonvulsants, and anaesthetics (may cause enhancement of the central depressive effect)
- Anti-epileptics drugs (causes depression and elevation of drug levels).

- Muscle relaxants
  One should be prepared for an increase of the muscle relaxing effect {risk of falls} when lorazepam is used during therapy with a muscle relaxant, especially during the beginning of treatment with lorazepam.
- Narcotic analgesics (enhancement of euphoria induced by narcotic analgesics may occur with benzodiazepine use, leading to an increase in psychic dependence).
- Clozapine concomitant administration has been reported to result in marked sedation, excessive salivation, hypotension, ataxia, delirium and an increased risk of respiratory and/or cardiac arrest.

- Loxapine: concomitant administration has led to reports of excessive stupor, significant reduction in respiratory rate, and in one patient, hypotension.

- Cisapride, lofexidine, nabilone, disulfiram and the muscle relaxants – baclofen and tizanidine enhances sedative effect.
- Hepatic enzyme inhibitors: compounds that inhibit certain hepatic enzymes, particularly cytochrome P450 such ascimetidine, isoniazid, erythyromycin, omeprazole, esomeprazole, itraconazole, ketoconazole, may enhance the activity of benzodiazepines. To a lesser extent this also applies to benzodiazepines that are metabolised by conjugation alone.
- Rifampicin may increase clearance of benzodiazepines.
- Antihypertensives, vasodilators and diuretics (enhanced hypotensive effect).
- Dopaminergics (possible antagonism of the effect of levodopa).
- Antacids (delays the absorption of lorazepam).
- Oestrogen-containing contraceptives (Possible inhibition of hepatic metabolism of lorazepam)
- Theophylline/aminophylline (administration may reduce the sedative effects of benzodiazepines, including lorazepam).
- Caffeine (Concurrent use may result in reduced sedative and anxiolytic effects of lorazepam).
- Sodium valproate: concurrent administration with lorazepam may result in increased plasma concentrations and reduced clearance of lorazepam. Therefore lorazepam dosage should be reduced to approximately 50 % when co-administered with sodium valproate.
- Probenecid: concurrent administration with lorazepam may result in a more rapid onset, or prolonged effect of lorazepam due to increased half-life and decreased total clearance. Lorazepam dosage should be reduced by approximately 50 % when co-administered with probenecid.

4.6 Fertility, pregnancy and lactation

Pregnancy:

There are insufficient data on the use of lorazepam during 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. Based on human experience lorazepam is

suggested / suspected to cause an increased risk of congenital malformations when administered during pregnancy, especially during the first trimester of pregnancy. In man, umbilical cord blood samples indicate placental transfer of benzodiazepines and their glucuronide metabolites.
Women of childbearing potential should use effective contraception during treatment with lorazepam. If the drug is prescribed to a woman of childbearing potential, she should be warned to contact her doctor about stopping the medicinal product if she intends to become, or suspects that she is, pregnant.
If, for compelling medical reasons, lorazepam is administered during the late phase of pregnancy, or during labour at high doses, effects on the neonate, such as hypothermia, hypotonia and moderate respiratory depression, can be expected, due to the pharmacological action of the compound. 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.
Moreover, infants born to mothers who took benzodiazepines chronically during the latter stages of pregnancy may have developed physical dependence and may be at some risk for developing withdrawal symptoms in the postnatal period.

Lactation:

There is evidence that lorazepam is excreted, albeit in pharmacologically insignificant amounts, in human breast milk. Therefore lorazepam should not be given to breast feeding 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 administered 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

Lorazepam has major influence on the ability to drive and use machines. Patients should be advised that sedation, amnesia, impaired concentration, dizziness, 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 also 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 medical 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.

Adverse reactions are listed with the following frequency categories

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

Blood and lymphatic system disorders
Very rare: Agranulocytosis, pancytopenia thrombocytopenia, leucopenia,
Not known: hyponatraemia

Immune system disorders
Very rare: anaphylactic/anaphylactoid reactions
Not known: angioedema, hypersensitivity reactions, allergic skin reactions

Endocrine disorders
Not known: Syndrome of Inappropriate Antidiuretic Hormone Hypersecretion (SIADH)

Psychiatric disorders
Common: confusion, depression, unmasking of depression
Rare: Behavioural effects include excitement, paradoxical aggressive outbursts and unmasking of depression with suicidal tendencies. If these occur Lorazepam should be discontinued.
Other rare effects are, numbed emotions, disinhibition, appetite changes, sleep disturbance, change in libido, decreased orgasm.

Not known: Drug dependence (see section 4.4), Suicidal ideation/attempt, euphoria.
Paradoxical reactions such as restlessness, anxiety, agitation, hostility, irritability, aggressiveness, delusion, rage, insomnia, nightmares, hallucinations, psychoses, and inappropriate behaviour have been occasionally reported during use. They are more likely to occur in children and the elderly.

Nervous system disorders[1]):
Very common: Sedation, drowsiness.
Common: Ataxia, dizziness
Rare: headache, reduced alertness, dysarthria/slurred speech, transient anterograde amnesia or memory impairment.
Very rare: Tremor, extrapyramidal reactions, Coma (see 4.9 Overdose)
Not known: convulsions / seizures, impaired attention / concentration, balance disorder, vertigo.

Eye disorders
Rare: Visual disturbances including diplopia and blurred vision

Vascular disorders
Rare: Hypotension , lowering of blood pressure (see 4.4 Special warnings and precautions)

Respiratory, thoracic and mediastinal disorder[2]):
Rare: Respiratory depression (see 4.9 Overdose). Apnoea, worsening of sleep apnoea, worsening of obstructive pulmonary disease,
Not known: Dysarthria/slurred speech.

Gastrointestinal disorders
Rare: Nausea, constipation, salivation changes

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

Skin and subcutaneous tissue disorders
Rare: Rash, allergic dermatitis
Not known: alopecia

Musculoskeletal and connective tissue disorders
Common: Muscle weakness,

Reproductive system and breast disorders
Uncommon: Impotence, change in libido, decreased orgasm

Not known: sexual arousal

General disorders and administration site conditions;
Very common: Fatigue
Common: Asthenia
Very rare: Hypothermia
Not known: Drug withdrawal symptoms (see section 4.4)

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.

1) – Benzodiazepine effects on the CNS are dose dependent, with more severe CNS depression occurring with high doses
2) – the extent of respiratory depression with benzodiazepines is dose dependent, with more severe depression occurring with high doses

Pre – existing depression may emerge during benzodiazepine use.
Transient anterograde amnesia or memory impairment may occur using therapeutic doses, the risk increasing at higher doses (see section 4.4).
Paradoxical reactions such as restlessness, agitation, irritability, aggressiveness, delusion, rage, nightmares, hallucinations, psychoses, and inappropriate behaviour have been reported occasionally during benzodiazepine use. Such reactions may be more likely to occur in children and the elderly (see section 4.4).
Use, even at therapeutic doses, may lead to physical or psychological dependence and discontinuation of therapy may result in withdrawal reactions or rebound phenomena (see section 4.4). Psychic dependence may occur.
Abuse of benzodiazepines has been reported.

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.

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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 **Overdose**

General:
As with other benzodiazepines, overdose should not present a threat to life unless combined with other CNS depressants, including alcohol.
In the management of overdose with any medicinal product, it should be borne in mind that multiple agents may have been taken. In post marketing experience, overdose with lorazepam has occurred predominantly in combination with alcohol and / or other medicinal products.

Patients should be informed of the signs and symptoms of overdose and to ensure that family and friends are also aware of these signs and to seek immediate medical help if they occur.

Symptoms:

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 where alcohol or other CNS depressant medicinal products are ingested, symptoms may include dysarthria, ataxia, paradoxical reactions, CNS depression, hypotension, hypotonia, respiratory and cardiovascular depression, rarely coma, and very rarely death.

Treatment:
Following overdose with oral benzodiazepines vomiting should be induced (within one hour), or if the patient is unconscious, Gastric lavage should be undertaken with the airway protected.
If there is no advantage in emptying the stomach, activated charcoal should be administered to reduce absorption. Thereafter treatment should be symptomatic and supportive.
The patient should be maintained under close observation, with monitoring of vital signs.
Respiratory and cardiovascular functions should be carefully monitored in intensive care. Hypotension, though unlikely, may be controlled with noradrenaline.
Lorazepam is poorly dialysable; lorazepam glucuronide, the inactive metabolite, may be highly dialysable.
The benzodiazepine antagonist, flumazenil may be useful in hospitalised patients as an adjunct to, not as a substitute for, the management of benzodiazepine overdose. Flumazenil product information should be consulted prior to use. The doctor should be aware of a risk of seizure in association with flumazenil therapy, especially in long term benzodiazepine users and in cyclic antidepressant overdose

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Benzodiazepine derivatives
ATC code: N05BA06

Lorazepam is a short acting benzodiazepine with anxiolytic, anticonvulsant, Skeletal muscle relaxant and sedative-hypnotic activity. The benzodiazepines are believed to act as agonists at the benzodiazepine receptor (BZ1 and BZ2) in the brain. Through the BZ-GABA receptor-chloride ionopore complex, they facilitate or amplify the inhibitory activity of GABA.

5.2 Pharmacokinetic properties

Lorazepam is readily absorbed from the gastro-intestinal tract following oral Administration, with a bioavailability of about 90%, peak plasma concentration is reported to occur in about 2 hours after an oral dose. The half life has been reported to range from 10 to 20 hours. Lorazepam is metabolised in the liver to the inactive glucuronide, and excreted in Urine. It is about 85% bound to plasma protein.

There is no alteration in the pharmacokinetic parameters in the elderly.

In severe hepatic impairment the elimination half-life of lorazepam is doubled. Renal impairment results in a decrease in rate of glucuronide metabolite excretion without an increase in the half-life of lorazepam.

5.3 Preclinical safety data

Single dose toxicity / Acute toxicity
Acute peroral lorazepam toxicity studies in animals did not reveal any specific sensitiveness (see 4.9 “Overdose” for acute toxicity in man).

Subchronic and chronic toxicity
Peroral lorazepam was investigated in rats (80 weeks) and dogs (12 months) in chronic toxicity studies. Histopathological, ophthalmological, and haematological examinations as well as organ functioning tests showed no or only slightly significant changes without biological relevance, even in high doses
Oesophageal dilation occurred in rats treated with lorazepam for more than one year at a dose of 6 mg /kg/day.

Mutagenic and carcinogenic potential
Lorazepam has not been subjected to extensive studies on mutagenic effects; however, tests on lorazepam were negative hitherto. Studies in rats and mice did not indicate any distinct carcinogenic potential after oral lorazepam application.

Reproduction toxicity
The effect of lorazepam on embryonal and foetal development and reproduction was examined in rabbits, rats and mice. These studies did notreveal any evidence of teratogenic properties or dysfunction of reproduction of lorazepam.
Experimental studies gave evidence of behavioural disorders of the offspring of maternal animals with long-term exposure to benzodiazepines.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose
Starch
Colloidal silicon dioxide
Sodium Starch Glycollate
Magnesium stearate
Aluminium lake patent blue V (E131)

6.2 Incompatibilities

None known.

6.3 Shelf life

60 months.

6.4 Special precautions for storage

Store below 25°C. Protected from moisture and light

6.5 Nature and contents of container

Polypropylene securitainers with snap secure lids, containing lorazepam tablets. (Material of the container complies with EEC directives for plastic in contact with Food and drug stuff)

Blister packs of 0.25mm PVC and 0.020mm Aluminium Foil.

Pack sizes: 14, 28, 30, 50, 56, 100, 250, 500, & 1000

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

None

7 MARKETING AUTHORISATION HOLDER

Pharmvit Limited
177 Bilton Road, Perivale
Greenford, Middlesex,
UB6 7HQ

8 MARKETING AUTHORISATION NUMBER(S)

PL 04556/0019

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

09/03/2009

10 DATE OF REVISION OF THE TEXT

16/01/2026