SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Lorazepam 0.5 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 0.5 mg of lorazepam.

Excipient(s) with known effect

Each tablet contains 32.06 mg of lactose monohydrate per tablet. For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

The tablets are light blue in colour, round, biconvex tablets, with "LZ" printed on one side and plain on the other. These tablets have a diameter of 5.1 mm ± 10%.

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 5 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

Posology

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

Pre-medication before operative dentistry or general surgery:

2-3 mg the night before operation, 2-4 mg one to two hours before the procedure.

Elderly and debilitated patients

For the elderly and debilitated patients reduce the initial dose by approximately 50% and adjust the dosage as needed and tolerated (see section 4.4).

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 the active substance, benzodiazepines or to any of the excipients listed in section 6.1
- 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))
- Myasthenia gravis
- 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.

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 section 4.8). 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 effects 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 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 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 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 section 4.8).

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 patient 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).

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

Elderly patients

Lorazepam should be used with caution in the 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).

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 lorazepam

Cisapride, lofexidine, nabilone, disulfiram and the muscle relaxants – baclofen and tizanidine.

Compounds that affect hepatic enzymes (particularly cytochrome P450)

- Inhibitors (e.g. cimetidine, isoniazid; erythromycin; 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 benzodiazepines. The effects of benzodiazepines 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

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.

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.

Breast-feeding

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.

Fertility

No fertility data is available.

4.7 Effects on 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 to 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 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.

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)

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: Thrombocytopenia, leucopenia, agranulocytosis, pancytopenia.

Immune system disorders

Very rare: Hypersensitivity including anaphylaxis/anaphylactoid reactions.

Endocrine disorders

Very rare: Inappropriate antidiuretic hormone secretion, hyponatraemia.

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

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 section 4.9).

Eye disorders

Rare: Visual disturbances (diplopia, blurred vision).

Vascular disorders

Rare: Hypotension (see section 4.4).

Respiratory, thoracic and mediastinal disorders

Rare: Apnoea, worsening of sleep apnoea, worsening of obstructive pulmonary disease. Respiratory depression (see section 4.9).

Gastrointestinal disorders

Rare: Nausea, constipation, salivation changes.

Hepatobiliary disorders

Rare: Abnormal liver function test values (increases in bilirubin, transaminases, alkaline phosphatise), 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 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.

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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

In the management of overdosage 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, hypotonia, 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 overdosage. Flumazenil product information should be consulted prior to use.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Nervous system; psycholeptics; anxiolytics;

benzodiazepine derivatives

ATC code: N05BA06

Lorazepam is a benzodiazepine with anxiolytic, sedative, hypnotic properties.

5.2 Pharmacokinetic properties

Absorption

Lorazepam is almost completely absorbed from the gastrointestinal tract and peak serum levels are reached in 2 hours.

Biotransformation

It is metabolised by a simple one- step process to a pharmacologically inert glucuronide. There are no major active metabolites.

Elimination

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 6 mg/kg/day.

Non-clinical data reveal no special hazard for humans based on conventional studies of single and repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development. However, behavioural disturbances were noted in offspring following longer benzodiazepine exposure of the dams.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Indigo carmine (E-132),

polacrilin potassium,

lactose monohydrate,

microcrystalline cellulose

magnesium stearate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 25ºC.

Store in the original package in order to protect from light.

6.5 Nature and contents of container

Aluminum/PVC-ACLAR ® (PCTFE) blisters in packages of 28 tablets.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Consilient Health Limited
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8 MARKETING AUTHORISATION NUMBER(S)

PL 24837/0170

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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