SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

LORAZIUM/Lorazepam Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Lorazepam BP 2.50 mg

3 PHARMACEUTICAL FORM

Tablet

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Anxiety

Benzodiazepines are only indicated for the short term relief (2 – 4 weeks only) of anxiety that is severe, disabling or subjecting the individual to extreme distress, occurring alone or in association with insomnia or short-term psychosomatic, organic or psychotic illness.

Insomnia

Benzodiazepines are only indicated when the insomnia is severe, disabling or subjecting the individual to extreme distress.

4.2 Posology and method of administration

Prior to starting treatment with LORAZIUM, a discussion should be held with patients to put in place a strategy for ending treatment with LORAZIUM 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.

Anxiety

Treatment should be as short as possible. The patient should be reassessed regularly and the need for continued treatment should be evaluated, especially in the case the patient is symptom free. The overall duration of treatment generally should not be more than 2 - 4 weeks, including a tapering off process.
In certain cases, extension beyond the maximum treatment period may be necessary; if so, it should not take place without re-evaluation of the patient's status with special expertise.

Insomnia

Treatment should be as short as possible. Generally, the duration of treatment varies from a few days to two weeks with a maximum, including tapering off process of four weeks.
In certain cases, extension beyond the maximum treatment period may be necessary; if so, it should not take place without the re-evaluation of the patient's status.
For all products: treatment should be started with the lowest recommended dose. The maximum dose should not be exceeded.
The method of administration is by the oral route.

Adults dosage:

Anxiety:

1-4 mg daily in divided doses. Start with a low dose and increase gradually to achieve symptom control.

Insomnia associated with anxiety:

1-2 mg at bedtime, for administration when required rather than regular use.

Phobic and Obsessional/Compulsive State:

1-4 mg daily in divided doses. Start with a low dose and increase gradually to achieve symptom control.

Premedication:

Preferably to be given the night before surgical or dental procedures, 2-3 mg. This dosage may be repeated one or two hours before operation and increased, if necessary, to 4 mg.
In the case of dental treatment as opposed to dental surgery 1-2.5 mg one-and-a-half hours to two hours before the treatment.

Elderly and patients with impaired liver and/or renal function:

Half the normal adult dose may be sufficient for a therapeutic response in the elderly.

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).**

Children:

Not recommended for children.

4.3 Contraindications

Myasthenia gravis. Hypersensitivity to benzodiazepines. Severe respiratory insufficiency. Sleep apnoea syndrome. Severe hepatic insuffiency.

LORAZIUM should not be given to patients with a sensitivity to the benzodiazepine group of drugs.

4.4 Special warnings and precautions for use

Tolerance

Some loss of efficacy to the hypnotic effects of benzodiazepines may develop after repeated use for a few weeks.

Drug dependence, tolerance and potential for abuse

Use of benzodiazepines may lead to the development of physical and psychic dependence upon these products. The risk of dependence increases with dose and duration of treatment; it is also greater in patients with a history of alcohol or drug abuse.

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).

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.

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.

Once physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms. These may consist of headaches, muscle pain, extreme anxiety, 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.

Rebound insomnia and anxiety: a transient syndrome 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.

Duration of treatment

The duration of treatment should be as short as possible (see Posology) depending on the indication, but should not exceed 4 weeks, including a tapering off process.

Extension beyond these periods should not take place without re-evaluation of the situation.

Withdrawal phenomena can become manifest within the dosage interval, especially when the dosage is high.

Amnesia

Benzodiazepines may induce anterograde amnesia. The condition occurs most often after several hours after ingesting the product and therefore to reduce the risk patients should ensure that they will be able to have an uninterrupted sleep of 7-8 hours (see also Undesirable Effects).

Psychiatric and paradoxical reactions

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. Should this occur, use of the medicinal product should be discontinued.

They are more likely to occur in children and the elderly.

Specific patient 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.

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).

A lower dose is also recommended for patients with chronic respiratory insufficiency due to the risk of respiratory depression. Benzodiazepines are not indicated to treat patients with severe hepatic insufficiency as they may precipitate encephalopathy.

Benzodiazepines are not recommended for the primary treatment of psychotic illness.

Benzodiazepines should not be used alone to treat depression or anxiety associated with depression (suicide may be precipitated in such patients).

Benzodiazepines should be used with extreme caution in patients with a history of alcohol or drug abuse.

4.5 Interaction with other medicinal products and other forms of interaction

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

Enhancement of the central depressive effect may occur in cases of concomitant use with antipsychotics (neuroleptics), hypnotics, anxiolytics/sedatives, antidepressant agents, narcotic analgesics, anti-epileptic products, anaesthetics and sedative antihistamines.

In the case of narcotic analgesics, enhancement of the euphoria may also occur leading to an increase in psychic dependence.

Compounds which inhibit certain enzymes (particularly cytochrome P450) may enhance the activity of benzodiazepines. To a lesser degree this also applies to benzodiazepines that are metabolised only by conjugation.

4.6 Pregnancy and lactation

If the product is prescribed to a woman of childbearing potential, she should be warned to contact her physician regarding discontinuance of the product if she intends to become or suspects that she is pregnant.

If, for compelling medical reasons, the product 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.

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.

Since benzodiazepines are found in the breast milk, benzodiazepines should not be given to breast feeding mothers.

4.7 Effects on ability to drive and use machines

Lorazepam can impair cognitive function and can affect a patient's ability to drive or to use machines 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

If insufficient sleep duration occurs, the likelihood of impaired alertness may be increased (see also Interactions).

4.8 Undesirable effects

Drowsiness, numbed emotions, reduced alertness, confusion, fatigue, headache, dizziness, muscle weakness, ataxia or double vision. These phenomena occur predominantly at the start of therapy and usually disappear with repeated administration. Other adverse reactions like gastrointestinal

disturbances, changes in libido or skin reactions have been reported occasionally.

Amnesia

Anterograde amnesia may occur using therapeutic dosages, the risk increasing at higher dosages. Amnestic effects may be associated with inappropriate behaviour. (See Warnings and Precautions).

Depression

Pre-existing depression may be unmasked during benzodiazepine use.

Psychiatric and paradoxical reactions

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 or benzodiazepinelike agents. They may be quite severe with this product. They are more likely to occur in children and the elderly.

Drug dependence (see section 4.4)

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.

Use (even at therapeutic doses) may lead to the development of physical dependence: discontinuation of the therapy may result in withdrawal or rebound phenomena (see Warnings and precautions). Psychic dependence may occur. Abuse of benzodiazepines has been reported.

<u>Reporting of suspected adverse reactions</u>

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

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.
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.
Following overdose with oral benzodiazepines, vomiting should be induced (within one hour) if the patient is conscious or gastric lavage undertaken with the airway protected if the patient is unconcious. If there is no advantage in emptying the stomach, activated charcoal should be given to reduce absorption. Special attention should be paid to respiratory and cardiovascular functions in intensive care.
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, symptoms may include ataxia, hypotonia, hypotension, respiratory depression, rarely coma and very rarely death.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Lorazepam is effective in alleviating the symptoms of pathological of pathological anxiety in anxiety states, and in anxiety associated with other psychiatric disorders. In general it should not be used in non-pathological anxiety where it may inhibit rather than enhance psychological adjustment. In the case of mixed depression and anxiety the therapeutic effect is on the anxiety symptoms only.

Lorazepam is an agonist at benzodiazepine receptors in the Central Nervous System. The CNS depression produced by Lorazepam is dose-related. An oral dose of 5mg produces obvious sedation and, in addition, an oral dose of 5mg produces anterograde amnesia. Lorazepam produces dose-related impairment of psychomotor function, e.g. critical flicker fusion frequency and reaction time. Lorazepam produces no significant change in blood pressure, pulse rate, ECG or cardiac output.

5.2 Pharmacokinetic properties

Following oral administration Lorazepam is absorbed from the gastro-intestinal tract. Peak plasma level is reached after approximately 2 hours and oral bio-availability of Lorazepam averages 90%. The mean half-life of Lorazepam elimination in humans is 15 hours with the usual range of 8 to 25 hours in healthy individuals.

The half-life is not impaired by the ageing process or renal disease, but may be prolonged in the case of hepatic dysfunction.

The volume of distribution is 1-21.ag.

The plasma protein binding is 88 to 92%.

The major metabolic pathway of Lorazepam in humans involves conjugation at the III position with glucoronic acid in the liver. This yields a water-soluble metabolite which is pharmacologically inactive and is eliminated mainly by renal excretion. Up to 75% of the dose is excreted as this metabolite within 5 days. The other metabolites of Lorazepam are hydroxylorazepam, quinazoline, carboxylic acid derivatives; these metabolites are not responsible for the pharmacological effect to any significant degree.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline Cellulose
Lactose
Talc
Sodium Starch Glycollate
Magnesium Stearate
Erythrosine Aluminium Lake E127

6.2 Incompatibilities

None known.

6.3 Shelf life

The shelf-life of LORAZIUM tablets 1 mg packaged for sale:

In plastic containers: 36 months.
In blister-strips: 24 months.

6.4 Special precautions for storage

Store below 25°C in a dry place in well closed containers.

6.5 Nature and contents of container

High density polystyrene with polythene lids and/or polypropylene containers with polypropylene or polythene lids and polyurethane or polythene inserts.

Packs of 100 and 500 tablets.

PVC/Aluminium foil blisters composed of 250 micron PVC glass-clear/bluish rigid PVC (pharmaceutical grade), and 20 micron hard tempered aluminium foil, coated on the dull side with 6-7 gsm heat-seal lacquer and printed on the bright side.

Packs of 28 tablets.

6.6 Special precautions for disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

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