SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Lorazepam tablets 2.5mg.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2.5mg tablet contains lorazepam BP 2.5mg.

3 PHARMACEUTICAL FORM

Tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Lorazepam Tablets are an anxiolytic of the benzodiazepine group, indicated for the short-term treatment of anxiety, alone or in association with insomnia, only when it is severe, disabling or subjecting the patient to extreme distress.

Lorazepam may also be used as premedication before operative dentistry and as a sedative for the anxious dental patient and as premedication before general surgery.

4.2 Posology and method of administration

Anxiety and Phobia
The maximum dose should be limited to 4mg daily for the short term treatment of severe and disabling cases of anxiety and phobia.

Insomnia
The maximum dose should be limited to 2mg daily for the short term treatment of severe insomnia.

Treatment should be as short as possible. The patient should be reassessed regularly and the need for continued treatment should be evaluated, especially in 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 specialist expertise.
Since associated insomnia is often transient and intermittent, the prolonged administration of lorazepam is generally not necessary and not recommended.

Dosage:

Adults:	
Anxiety and Phobia	1mg to 4mg daily in divided doses. If insomnia is present, 1mg to 2mg of the dose should be taken before retiring.
Insomnia:	1mg to 2mg of the dose should be taken before retiring.
Premedication:	2mg to 3mg the night before operation, 2mg to 4mg 1 to 2 hours before operation.
Elderly:	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:	
(aged 5-13 years):	Lorazepam Tablets are not recommended for the treatment of anxiety in children.
Premedication:	0.5mg to 2.5mg or 0.05mg/kg to the nearest 0.5mg according to weight, not less than one hour before operation.
Dentistry:	1mg to 2.5mg, 1½ to 2 hours before dental treatment. For operative dentistry dosage as for premedication.
Patients with impaired hepatic and renal function:	Lower doses may be sufficient in these patients. Use in patients with severe hepatic impairment is contra-indicated.
Route of administration:	Oral.

4.3. Contra-indications

Lorazepam Tablets are contraindicated in patients with known sensitivity to benzodiazepines, myasthenia gravis, severe respiratory insufficiency, sleep apnoea syndrome and severe hepatic insufficiency.

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.

Dependence
Use of benzodiazepines may lead to the development of physical and psychological 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.
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 section 4.2 Posology and method of administration) depending on the indication, but should not exceed 2 to 4 weeks including 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.
Amnesia
Benzodiazepines may induce anterograde amnesia. The condition occurs most often 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 section 4.8 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 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.
Caution should be exercised when administering to patients with renal insufficiency or muscular weakness.
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 or personality disorder.
The use of Benzodiazepines for the treatment of mild anxiety is not recommended.
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).

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

4.5 Interaction with other medicinal products and other forms of interaction

- Not recommended: Concomitant intake with alcohol.

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

- Take into account: Combination with CNS depressants.

  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 psychological dependence.

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

The antibacterial agent rifampicin may increase the metabolism of benzodiapines such as lorazepam.

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).

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 develop physical dependence and may be at some risk of 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

Sedation, amnesia, impaired concentration and impaired muscular function may adversely affect the ability to drive or to use machines. If insufficient sleep duration occurs, the likelihood of impaired alertness may be increased (see also section 4.5 Interactions with other medicaments and other forms of interaction).

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:
    - o The medicine has been prescribed to treat a medical or dental problem and
    - o You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
    - o It was not affecting your ability to drive safely.

4.8. Undesirable effects

Drowsiness during the day, numbed emotions, reduced alertness, confusion, fatigue, headache, dizziness, vomiting and nausea, salivation changes, dysarthria, muscle weakness, tremors, ataxia or visual disturbances for example double vision. These phenomena occur predominately at the start of therapy and usually disappear with repeated administration. Other adverse reactions like gastrointestinal disturbances, changes in libido, blood disorders or jaundice, or skin reactions have been reported occasionally.

Amnesia

Anterograde amnesia may occur using therapeutic dosages, the risk increasing at higher dosages. Amnesic effects may be associated with inappropriate behaviour (see section 4.4 Special warnings and special precautions for use).

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

Dependence

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 section 4.4 Special warnings and special precautions for use). Psychological dependence may occur. Abuse of benzodiazepines has been reported.

4.9. Overdose

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 unconscious. 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.

Flumazenil may be useful as an antidote.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

5.2. Pharmacokinetic properties

Following oral administration, lorazepam is absorbed from the gastrointestinal tract, and it achieves a bioavailability of about 90%. Peak plasma concentrations are reached approximately 2 hours after the oral dose.

It is reported that the mean half life is 15 hours with a range from 8 to 25 hours. The half life is not affected by renal disease or the ageing process, but

may be prolonged in the case of hepatic dysfunction. Lorazepam is mainly metabolised into the inactive glucuronide in the liver and it is then excreted in the urine. Up to about 75% of the dose is excreted as this metabolite within 5 days. A small proportion of lorazepam is metabolised by other routes to hydroxylorazepam or to quinazolinine or quinazoline carboxylic acid derivatives. The metabolites are not responsible for the pharmacological effect to any significant degree, which is not consistent with other benzodiazepines.

The degree of protein binding of lorazepam is about 85% to 92%.

One study performed suggested that lorazepam does cross the placental barrier, but not as readily as diazepam. Foetal concentration of lorazepam rarely exceeded that of the mother, and following delivery, the neonates were able to metabolise lorazepam at the same rate as the mother.

It is reported that in a study including 4 lactating mothers who had received 3.5mg lorazepam by mouth as premedication, free lorazepam concentrations in the breast milk ranged from 8ng to 9ng per ml 4 hours after the dose, this represented approximately 15% to 26% of the concentration in plasma which was considered to be sufficiently low to cause no adverse effects in breast-fed infants.

References

1. Martindale The Extra Pharmacopoeia 29th Edition, The Pharmaceutical Press.

2. Therapeutic Drugs (Volume 2) edited by Sir Colin Dollery. Churchill Livingston.

A comparative *in-vivo* bioavailability study was carried out comparing Lagap Lorazepam with Ativan*. The following results were obtained for the Lagap product:

Mean peak plasma level ± SE	=	34.21ng/ml ± 3.07ng/ml
Mean time to peak level ± SE	=	2.44 hours ± 0.88 hours
Mean AUC ± SD	=	675.1ng/ml hour ± 203.4ng/ml

5.3. Preclinical safety data

There are no preclinical safety data of relevance to the prescriber.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose, microcrystalline cellulose, talc, sodium starch glycollate and indigo carmine lake (E132).

6.2. Incompatibilities

None known.

6.3. Shelf Life

Securitainers: 24 months
Blister pack: 12 months

6.4. Special Precautions for Storage

Store in a cool dry place. Protect from light.

6.5. Nature and Contents of Container

Securitainers pack sizes: 28, 100 and 500.
Polyethylene/aluminium blister pack sizes: 28, 30 and 100.

6.6. Instructions for Use/Handling

Not applicable.

7 MARKETING AUTHORISATION HOLDER

Sandoz Ltd
Frimley Business Park
Frimley
Camberley
Surrey
GU16 7SR
UK

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PL 4416/0095

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05/10/2006

10 DATE OF REVISION OF THE TEXT

25/04/2019