IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA1332/026/001
Case No: 2050567

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Transferred from PA0022/037/002.

Meda Health Sales Ireland Limited

Office 10, Dunboyne Business Park, **Dunboyne**, **Co. Meath**, **Ireland**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Loramet 1.0mg Tablets

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **02/05/2008** until **09/01/2010**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Loramet 1.0mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 1.0 mg lormetazepam.

For excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet
Circular, white uncoated tablets embossed ‘WYETH’ on one face ‘WY037’ on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the short term treatment of insomnia when it is disabling or subjecting the individual to extreme distress.

4.2 Posology and method of administration

Dosage and duration of therapy should be individualised. The lowest effective dose should be prescribed for the shortest duration possible. This may vary from a few days to two weeks with a maximum, including tapering off period, of four weeks. The risk of withdrawal and rebound phenomena is greater after abrupt discontinuation; therefore the drug should be discontinued gradually.

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.

Adults:
0.5mg to 1.0mg before bedtime, depending on the severity of the condition.

Elderly:
Elderly patients may be better on lower dosage and less frequent use. A dose of 0.5mg may be sufficient. Duration of treatment should be as short as possible.

Children:
Lormetazepam is not recommended for use in children.

Use in patients with hepatic impairment:
Loramet is contraindicated in severe hepatic insufficiency. Dosage for patients with mild to moderate hepatic insufficiency should be reduced and adjusted carefully according to patient response.

Use in patients with renal impairment:
No specific dosage recommendations.

4.3 Contraindications

Myasthenia gravis.
Hypersensitivity to benzodiazepines or any component of the product.
Severe respiratory insufficiency.
Sleep apnoea syndrome.
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 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.

Once physical dependence has developed, abrupt termination of treatment may be accompanied by withdrawal symptoms. Symptoms reported following discontinuation of benzodiazepines include headaches, muscle pain, extreme anxiety, tension, depression, insomnia, restlessness, confusion, irritability, sweating, rebound phenomena, dysphoria, dizziness, derealization, depersonalization, hyperacusis, numbness/tingling of extremities, hypersensitivity to light, noise and physical contact/perceptual changes, involuntary movements, nausea, vomiting, diarrhoea, loss of appetite, hallucinations/delirium, convulsions/seizures, tremor, abdominal cramps, myalgia, agitation, palpitations, tachycardia, panic attacks, vertigo, hyperreflexia, short-term memory loss, and hyperthermia. Convulsions/seizures 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.

Rebound insomnia and anxiety
A transient syndrome whereby the symptoms that led to treatment with a benzodiazepine may 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 and Method of Administration) depending on the indication, but should not exceed 4 weeks for insomnia 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.

When benzodiazepines of 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 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 drug 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 should be kept to a minimum. Elderly or debilitated patients may be more susceptible to the effects of lormetazepam; therefore, these patients should be given a reduced dose and be monitored frequently. Dosage should be adjusted carefully according to patient response.

Elderly patients should be warned of the risk of falls due to the myorelaxant effects of Loramet Tablets, particularly if they get up at night.

Use of benzodiazepine, including lormetazepam, may lead to potentially fatal respiratory depression. A lower dose is also recommended for patients with chronic respiratory insufficiency.

Benzodiazepines are not indicated to treat patients with severe hepatic insufficiency as they may precipitate encepalopathy.

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.

Patients with rare hereditary problems of galactose intolerance, the Lapp 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 effects may occur in cases of concomitant use with antipsychotics (neuroleptics), hypnotics, anxiolytics/sedatives, antidepressant agents, narcotic analgesics, antiepileptic drugs, anaesthetics and sedative antihistamines.
In the case of narcotic analgesics enhancement of the euphoria may also occur with benzodiazepines leading to an increase in psychic dependence.

Compounds which inhibit certain hepatic enzymes (particularly cytochrome P 450) may enhance the activity of benzodiazepines. To a lesser degree this also applies to benzodiazepines that are metabolised only by conjugation.

Administration of theophylline or aminophylline may reduce the sedative effects of benzodiazepines, including lormetazepam.

4.6 Pregnancy and lactation

Lormetazepam should not be used during pregnancy.
An increased risk of congenital malformations associated with the use of benzodiazepines during the first trimester of pregnancy has been suggested in several studies. In humans, umbilical cord blood samples indicate placental transfer of benzodiazepines and their glucuronide metabolites. 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.

If lormetazepam is given 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 she is pregnant.

Lormetazepam has been detected in human breast milk; therefore it should not be administered to breast-feeding women, unless the expected benefit to the woman outweighs the potential risk to the infant.

Sedation and inability to suckle have occurred in neonates of lactating mothers taking 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

Sedation, amnesia, impaired concentration and impaired muscular function may adversely affect the ability to drive or use machines. If insufficient sleep duration occurs, the likelihood of impaired alertness may be increased. Patients should be warned not to operate dangerous machinery or motor vehicles if any of these effects occur (see also Interaction with other Medicinal Products and Other Forms of Interaction).

4.8 Undesirable effects

Adverse reactions are listed in the following table in CIOMS frequency categories:

Very common	≥ 10%
Common	≥ 1%
Uncommon	≥ 0.1% and <1%
Rare	≥ 0.01% and <0.1%
Very rare	< 0.01%

Body as a whole:
Frequency undetermined: Hypersensitivity reactions, anaphylactic/anaphylactoid reactions, Syndrome of Inappropriate Antidiuretic Hormone (SIADH), hyponatraemia, hypothermia.

Common: Muscle weakness, asthenia.

Cardiovascular:
Frequency undetermined: Hypotension, lowering in blood pressure.

Digestive:
Uncommon: Nausea.

Frequency undetermined: Constipation, increase in bilirubin, jaundice, increase in liver transaminases, increase in alkaline phosphatase.

Haematological/lymphatic:
Frequency undetermined: Thrombocytopenia, agranulocytosis, pancytopenia.

Nervous system and special senses:
Frequency undetermined: Benzodiazepine effects on the CNS are dose dependent, with more severe CNS depression occurring with high doses.

Extrapyramidal symptoms, tremor, vertigo, visual disturbances (including diplopia and blurred vision), dysarthria/slurred speech, headache, convulsions/seizures; amnesia, disinhibition, euphoria, coma; suicidal ideation/attempt.

Paradoxical reactions including anxiety, agitation, excitation, hostility, aggression, rage, sleep disturbances/insomnia, sexual arousal, hallucinations.

Very common: Sedation, fatigue, drowsiness.
Common: Ataxia, confusion, depression, unmasking of depression, dizziness.
Uncommon: Change in libido, impotence, decreased orgasm.

Respiratory:
Frequency undetermined: Respiratory depression, apnoea, worsening of sleep apnoea (the extent of respiratory depression with benzodiazepines is dose dependent, with more severe depression occurring with high doses).

Worsening of obstructive pulmonary disease.

Skin:
Frequency undetermined: Allergic skin reactions, alopecia.

Amnesia
Anterograde amnesia may occur using therapeutic dosages, the risk increasing at higher dosages. Amnetic effects may be associated with inappropriate behaviour (see Special Warnings and Precautions for Use).

Depression
Pre-existing depression may be unmasked during benzodiazepine use.

Psychiatric and 'paradoxical'reactions
See Special Warnings and Precautions for Use

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 Special Warnings and Precautions for Use).

Psychic 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.

In post marketing experience, overdose with lormetazepam has occurred predominantly in combination with alcohol and/or other drugs.

Following overdose with oral benzodiazepines, general supportive and symptomatic measures are recommended; vital signs must be monitored. Vomiting should be induced (within one hour) if the patient is conscious or gastric lavage if the patient is unconscious. If there is no advantage in emptying the stomach, activated charcoal may be effective in reducing absorption. Special attention should be paid to respiratory and cardiovascular functions in intensive care.

When there is a risk of aspiration, induction of emesis is not recommended.

Lormetazepam is poorly dialysable. Lormetazepam glucuronide, the inactive metabolite, may be dialyzable;

The benzodiazepine antagonist, flumazenil may be useful in hospitalised patients as an adjunct to, not as a substitute for, proper management of benzodiazepine overdose. The physician should be aware of a risk of seizures in association with flumazenil treatment, particularly in long-term benzodiazepine users and in cyclic antidepressant overdose.

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

Pharmacotherapeutic Group: Hypnotics and Sedatives.
ATC Code: N05CD06.

Lormetazepam is a benzodiazepine with anxiolytic and hypnotic properties.

5.2 Pharmacokinetic properties

Lormetazepam is rapidly absorbed from the gastrointestinal tract and is metabolised by a simple one-step process to a pharmacologically inactive glucuronide. There are no major metabolites. Peak plasma levels are reached after 2 hours. Lormetazepam has a terminal phase half-life of about 11 hours. Clinical studies have shown minimal effects on REM sleep and on psychomotor performance on the day after treatment with lormetazepam.

5.3 Preclinical safety data

Nothing of relevance to the prescriber.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize starch
Povidone 2500
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

5 years.

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

Amber glass bottles or polypropylene securitainers containing 30 or 100 tablets. PVC/Aluminium foil blister strips of 10 tablets in outer cartons of 30 or 100 tablets.

Not all Pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Meda Health Sales Ireland Limited
Office 10
Dunboyne Business Park
Dunboyne
Co. Meath
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 1332/26/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10 January 1995

Date of last renewal: 10 January 2005

10 DATE OF REVISION OF THE TEXT

May 2008