

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Loprazolam 1mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Loprazolam Mesilate equivalent to 1mg Loprazolam.

Excipient(s) with known effect

Each tablet contains 41.855mg of lactose anhydrous.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

Light yellow, biconvex, round, uncoated tablets with 'L1' debossed on one side and deep break line on other side.

The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Loprazolam is indicated for the short-term treatment of insomnia including difficulty in falling asleep and/or frequent nocturnal awakenings. Benzodiazepines should be used to treat insomnia only when it is severe, disabling or subjecting the individual to extreme distress. An underlying cause of insomnia should be sought before deciding upon the use of benzodiazepines for symptomatic relief.

4.2 Posology and method of administration

Prior to starting treatment with Loprazolam, a discussion should be held with patients

to put in place a strategy for ending treatment with Loprazolam 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.

Posology

Adults

The recommended dose is 1mg at bedtime. This may be increased to 1.5mg or 2mg if necessary.

Elderly

Dosage in the elderly should be limited to 1mg at bedtime.

Frail, debilitated or aged patients

A starting dose of a half tablet may be appropriate. Dosage should not exceed 1mg.

Treatment should if possible be intermittent.

Dosage and duration of therapy should be individualized. The lowest dose to control symptoms should be used. Treatment should not normally be continued beyond 4 weeks.

Long term chronic use is not recommended.

Treatment should always be tapered off gradually.

Patients who have taken benzodiazepines for a long time may require a longer period during which doses are reduced.

Paediatric population

There is insufficient evidence to recommend the use of Loprazolam in children.

Method of administration

Oral

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Hypersensitivity to other benzodiazepines.

Acute pulmonary insufficiency.

Severe respiratory insufficiency.

Myasthenia gravis.

Phobic or obsessional states and sleep apnoea syndrome.

Monotherapy in depression or anxiety associated with depression and chronic psychosis and alcohol intake.

Severe hepatic insufficiency.

Pregnancy and lactation (see also 4.6 “Fertility, pregnancy and lactation”).

4.4 Special warnings and precautions for use

Psychiatric and paradoxical reactions

Benzodiazepines may cause reactions such as restlessness, agitation, irritability, aggressiveness, delusion, rages, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects. Should this occur, treatment should be discontinued.

These reactions are more common in children and the elderly, and in patients with organic brain syndrome.

Disinhibiting effects may be manifested in various ways. Suicide may be precipitated in patients who are depressed and who exhibit aggressive behaviour towards self and others. Extreme caution should therefore be used in prescribing benzodiazepines in patients with personality disorders.

Duration of treatment

The duration of treatment should be as short as possible (see also 4.2. “Posology and method of administration”). Generally it varies from a few days to two weeks with a maximum period of four weeks, including the time required for gradual withdrawal of the medication.

It may be useful to inform the patient when treatment is started that it will be of limited duration and to explain clearly how the dose will be gradually decreased.

Treatment must never be prolonged without re-assessment of the patient.

Drug dependence, tolerance and potential for 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 online, 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 loprazolam 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 loprazolam, 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 loprazolam 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.

Amnesia

Benzodiazepines may induce anterograde amnesia. The condition occurs most often several hours after administration of the product and therefore to reduce the associated risk, patients should ensure that they will be able to have uninterrupted sleep for 7-8 hours (see section 4.8 “Undesirable effects”). Loprazolam should be used with caution in chronic pulmonary insufficiency, cerebrovascular disease and chronic renal or hepatic impairment. Caution should be used in the treatment of patients with narrow-angle glaucoma.

Excipient

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

Risk from concomitant use of opioids:

Concomitant use of Loprazolam 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 Loprazolam with opioids should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Loprazolam 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).

Suicidality and depression

Several epidemiological studies show an increased incidence of suicide and suicide attempt in patients with or without depression, treated with benzodiazepines and other hypnotics, including loprazolam. A causal relationship has not been established.

Fall

Due to its pharmacological properties, lorazepam can cause drowsiness and a decreased level of consciousness, which may lead to falls and consequently to severe injuries, especially in elderly. (See Section 4.8)

4.5 Interaction with other medicinal products and other forms of interaction

Lorazepam may be potentiated by alcohol or other drugs acting on the CNS or with Cisapride. Additive synergy has been observed with neuromuscular depressants (curare-like drugs and muscle relaxants).

Combination with CNS depressants e.g. antipsychotics, hypnotics, anxiolytics/sedatives, antidepressant agents, narcotic analgesics, anti-epileptic drugs, anaesthetics and sedative antihistamines, causes enhancement of the central depressive effects of Lorazepam.

Concomitant intake with alcohol is not recommended. The sedative effects may be enhanced when the product is used in combination with alcohol. This affects the ability to drive or use machinery.

The risk of a withdrawal syndrome occurring is increased when Lorazepam is combined with other benzodiazepines prescribed as anxiolytics or hypnotics.

Benzodiazepines and 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 Fertility, 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.

Pregnancy

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 dependency and may be at some risk for developing withdrawal symptoms in the postnatal period.

Breast-feeding

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

4.7 Effects on ability to drive and use machines

Attention should be drawn to the risk of drowsiness, sedation, amnesia, impaired concentration and muscular weakness, especially in drivers of vehicles and operators of machines, when taking the product (see also “Interactions”).

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

In general, Loprazolam is very well tolerated. The following undesirable effects have been observed and reported during treatment with benzodiazepines with the following frequencies: Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

MedDRA System Organ Class	Frequency	Undesirable effects
Blood and lymphatic disorders	Very rare	Blood disorder
Psychiatric disorders	Rare	¹ Aggression, agitation, confusional state, uncovering depression, suicidal ideation
	Very rare	Libido disorder
	Not known	Psychological trauma, drug dependence (see section 4.4)
Nervous system	Common	Headaches, somnolence,

disorders	Not known	hypotonia, dizziness, ataxia Anterograde amnesia, speech disorders. In cases of loss or bereavement, psychological adjustment may be inhibited by benzodiazepines.
Eye disorders	Common Very rare	Blurred vision Visual impairment
Vascular disorders	Very rare	Hypotension
Gastrointestinal disorders	Common Very rare	Nausea Gastrointestinal disorders
Hepatobiliary disorders	Very rare	Jaundice
Skin and subcutaneous tissue disorders	Very rare	Rash
Renal and urinary disorders	Very rare	Urinary retention
Injury, poisoning and procedural complications	Not known	Fall (see Section 4.4)
General disorders and administration site conditions	Not known	Drug withdrawal symptoms (see 4.4 Special warnings and precautions)

¹If these reactions should occur, use of the drug should be discontinued.

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 or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

As with other benzodiazepines, overdosage does not usually present a threat to life. Treatment is symptomatic and gastric lavage may be of use if performed shortly after ingestion. Use of a specific antidote such as flumazenil in association with symptomatic treatment in hospital should be considered.

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Benzodiazepines, ATC code: N05CD11

Benzodiazepines have a widespread action as a result of their enhancing the release of gamma-amino butyric acid (GABA). They are effective as anti-convulsants, muscle relaxants, anti-anxiety agents, pre-medications and sedative hypnotics.

5.2 Pharmacokinetic properties

The pharmacokinetics of oral Loprazolam given in a single dose or in repeated doses on 7 consecutive nights were studied in a balanced cross-over trial in six healthy male subjects aged 22-37 years. The subjects were allocated randomly to the treatment phases which were separated by 2-week drug-free intervals. Loprazolam was administered as 1mg tablets.

On the night of administration of the single dose and the seventh repeated dose, venous blood samples were taken before and at intervals after treatment. Serum Loprazolam concentrations were measured using both a radioimmunoassay (RIA) and the more specific high pressure liquid chromatography and gas chromatography (HPLC/GC) technique. Maximum serum levels (C_{max}) and the time taken to achieve them (T_{max}) were measured, and the half-life ($t_{1/2}$) was calculated. The area under the

serum concentration-time curve (AUC) was determined using the trapezoidal rule. The ratios of AUC and $C_{\max}$ after repeated doses to AUC and $C_{\max}$ after single doses were used to assess possible accumulation of Loprazolam.

	MEAN (SD)	
SINGLE DOSES	RIA data	SINGLE DOSES
$C_{\max}$ (mcg/litre)	4.0 (1.2)	$C_{\max}$ (mcg/litre)
$t_{\max}$ (hours)	4.0 (2.1)	$t_{\max}$ (hours)
$t_{1/2}$ (hours)	11.7 (4.7)	$t_{1/2}$ (hours)
AUC (mcg/litre hour)	60.0 (20.9)	AUC (mcg/litre hour)
REPEATED DOSES	RIA data	REPEATED DOSES
$C_{\max}$ (mcg/litre)	5.1 (1.2)	$C_{\max}$ (mcg/litre)
$t_{\max}$ (hours)	5.3 (3.7)	$t_{\max}$ (hours)
$t_{1/2}$ (hours)	12.8 (4.9)	$t_{1/2}$ (hours)
AUC (mcg/litre hour)	75.6 (21.1)	AUC (mcg/litre hour)

n = 6 subjects, except for *n = 5, **n = 3.

5.3 Preclinical safety data

No additional data of relevance to the prescriber.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose Anhydrous

Microcrystalline Cellulose

Magnesium Stearate

6.2 Incompatibilities

None

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

Alu/PVC Blisters, packaged in cartons of 7, 10, 14, 15, 20, 28, 30 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Focus Pharmaceuticals Limited
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8 MARKETING AUTHORISATION NUMBER(S)

PL 20046/0295

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28/03/2014

10 DATE OF REVISION OF THE TEXT

12/02/2026