SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Molap 4 mg Film-coated Tablets

Lacidipine 4mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 4 mg lacidipine.

Excipient with known effect : 258,33 mg of Lactose Monohydrate in each film-coated tablet.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.
White, ovoidal biconvex film-coated tablets with a scoreline on both sides and embossed with ‘4’ on one side.
The tablet can be divided into two equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Lacidipine is indicated for the treatment of essential hypertension either alone or in combination with other antihypertensive agents, including ß-adrenoceptor antagonists, diuretics, and ACE-inhibitors.

4.2 Posology and method of administration

Posology

The treatment of hypertension should be adapted to the severity of the condition, and according to the individual response.

The recommended initial dose is 2 mg once daily. The dose may be increased to 4 mg (and then, if necessary, to 6 mg) after adequate time has been allowed for the full

pharmacological effect to occur. In practice, this should not be less than 3 to 4 weeks. Daily doses above 6 mg have not been shown to be significantly more effective.

Lacidipine should be taken at the same time each day, preferably in the morning.

The treatment with Lacidipine may be continued indefinitely.

Patients with hepatic impairment:

Lacidipine is metabolised primarily by the liver and therefore in patients with hepatic impairment, the bioavailability of Lacidipine may be increased and the hypotensive effect enhanced. These patients should be carefully monitored, and in severe cases, a dose reduction may be necessary.

Patients with renal impairment:

As Lacidipine is not cleared by the kidneys, the dose does not require modification in patients with kidney disease.

Pediatric population:

Since no experience has been gained with lacidipine in children, the administration of Lacidipine is not recommended in children and adolescents ≤18 years.

Elderly:

No dose adjustment is necessary in the elderly.

Method of administration

For oral administration

4.3 Contraindications

Lacidipine is contraindicated in patients with known hypersensitivity to the active substance or to any of the excipients listed in section 6.1. Lacidipine should only be used with great care in patients with a previous allergic reaction to another dihydropyridine because there is a theoretical risk of cross-reactivity.

In addition, dihydropyridines have been shown to reduce coronary arterial blood-flow in patients with aortic stenosis and in such patients Lacidipineis contraindicated.

As with other calcium antagonists, lacidipine should be discontinued in patients who develop cardiogenic shock and unstable angina.

Lacidipine should not be used during or within one month of a myocardial infarction and in case of severe left ventricular failure.

In case of rare hereditary conditions that may be incompatible with an excipient of the product (please refer to section 4.4 Special Warnings and Precautions for Use) the use of the product is contraindicated.

4.4 Special warnings and precautions for use

In specialised studies lacidipine has been shown not to affect the spontaneous function of the SA node or to cause prolonged conduction within the AV node. However, the

theoretical potential for a calcium antagonist to affect the activity of the SA and AV nodes should be noted, and therefore lacidipine should be used with caution in patients with pre-existing abnormalities in the activity of the SA and AV nodes.

As has been reported with other dihydropyridine calcium channel antagonists, lacidipine should be used with caution in patients with congenital or documented acquired QT prolongation. Lacidipine should also be used with caution in patients treated concomitantly with medications known to prolong the QT interval such as class I and III antiarrhythmics, tricyclic antidepressants, some antipsychotics, antibiotics (e.g. erythromycin) and some antihistamines (e.g. terfenadine).

As with other calcium antagonists, lacidipine should be used with caution in patients with poor cardiac reserve.

There is no evidence that lacidipine is useful for secondary prevention of myocardial infarction.

The efficacy and safety of lacidipine tablets in the treatment of malignant hypertension has not been established.

Lacidipine should be used with caution in patients with impaired liver function because antihypertensive effect may be increased.

There is no evidence that lacidipine impairs glucose tolerance or alters diabetic control.

This product contains Lactose Monohydrate. 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

Lacidipine is known to be metabolised by cytochrome CYP3A4 and, therefore, caution should be exercised when lacidipine is administered with drugs which inhibit the CYP 3A4 enzyme, such as ketoconazole, itraconazole, or with drugs which induce CYP 3A4, such as phenytoin, carbamazepin, phenobarbital and rifampicin and posology of lacidipine should be adjusted if needed.

Other antihypertensive agents

Co-administration of lacidipine with other agents recognised to have a hypotensive effect, including anti-hypertensive agents, (e.g. diuretics, beta-blockers or ACE-inhibitors), may have an additive hypotensive effect. However, no specific interaction problems have been identified in studies with common antihypertensive agents (e.g. beta-blockers and diuretics) or with digoxin, tolbutamide or warfarin.

The plasma level of lacidipine may be increased by simultaneous administration of cimetidine.

Alcohol

As with all antihypertensives (vasodilators) caution is recommended when alcohol is consumed since this may increase the effects.

Grapefruit juice

As with other dihydropyridines, lacidipine should not be taken with grapefruit juice as bioavailability may be altered.

Lacidipine is highly protein-bound (more than 95%) to albumin and alpha-1-glycoprotein.

In clinical studies in patients with a renal transplant treated with cyclosporin, lacidipine reversed the decrease in renal plasma flow and glomerular filtration rate induced by cyclosporin.

Concomitant use of lacidipine and corticoids or tetracosactide might decrease antihypertensive effect.

4.6 Fertility, pregnancy and lactation

Pregnancy*:*

There are no clinical data on the use of this drug in pregnant women.

Although some calcium channel blockers have been found to be teratogenic in animals, studies with lacidipine in animals have not shown malformations. At high doses, embryo-fetal lethality and toxicity were found in animals (see section 5.3). Lacidipine should only be used in pregnancy when the potential benefits for the mother outweigh the possibility of adverse effects in the fetus or neonate.

The possibility that lacidipine can cause relaxation of the uterine muscle at term should be considered (see section 5.3)

Breastfeeding:

Lacidipine and its metabolites are likely to be excreted into breast milk. Therefore the use of Lacidipine during lactation should be avoided.

Lacidipine should only be used during lactation when the potential benefits for the mother outweigh the possibility of adverse effects in the foetus or neonate.

Fertility:

Some patients treated with calcium channel blockers have reported reversible biochemical changes in the head of spermatozoa which can make fertilization difficult.

4.7 Effects on ability to drive and use machines

Lacidipine may cause dizziness. Patients should be warned not to drive or operate machinery if they experience dizziness or related symptoms.

4.8 Undesirable effects

Data from large clinical studies (internal and published) are used to determine the frequency of very common to uncommon side effects

Very common ≥1/10

Common ≥ 1/100, <1/10

Uncommon	≥ 1/1000, <1/100
Rare	≥ 1/10000, <1/1000
Very rare	<1/10000
Not known	Cannot be estimated from the available data

Lacidipine is generally well tolerated. Some individuals may experience minor side effects which are related to its known pharmacological action of peripheral vasodilation. Such effects, indicated by a hash (#), are usually transient and usually disappear with continued administration of Lacidipine at the same dosage.

Pysichiatric disorders

Depression	very rare

Nervous system disorders

Dizziness#	common
Headache#	common
Tremor	very rare

Cardiac disorders

Palpitations#	common
Tachycardia	common
Syncope	uncommon
Angina pectoris	uncommon

As with other dihydropyridines aggravation of underlying angina pectoris has been reported in a small number of individuals, especially at the start of treatment. This is more likely to happen in patients with symptomatic ischaemic heart disease. Lacidipine should be discontinued under medical supervision in patients who develop unstable angina.

Vascular disorders

Flushing#	common
Hypotension	uncommon

Gastrointestinal disorders

Abdominal discomfort	common
Nausea	common
Gingival hyperplasia	uncommon

Skin and subcutaneous tissue disorders

Rash	common
Erythema	common
Pruritus	common
Angioedema	rare
Urticaria	rare

Musculoskeletal and connective tissue disorders

Muscle cramps	rare

Renal and urinary disorders

Polyuria	common

General disorders and administration site conditions

Asthenia	common
Oedema#	common

Investigations:

Reversible increase in alkaline phosphatase (sometimes clinically significant increases)	common

Reporting of suspected adverse reaction

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

4.9 Overdose

Symptoms:

There have been no recorded cases of Lacidipine overdosage. The expected symptoms could comprise prolonged peripheral vasodilation associated with hypotension and tachycardia. Bradycardia or prolonged AV conduction could occur.

Therapy:

There is no specific antidote. Standard general measures for monitoring cardiac function and appropriate supportive and therapeutic measures should be used.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: dihydropyridine derivatives, ATC-code: C08CA09

Lacidipine is a specific and potent calcium antagonist with a predominant selectivity for calcium channels in the vascular smooth muscle. Its main action is to dilate peripheral arterioles, reducing peripheral vascular resistance and lowering blood pressure.

In a study of ten patients with a renal transplant, lacidipine has been shown to prevent an acute decrease in renal plasma flow and glomerular filtration rate about six hours after administering oral cyclosporin. During the trough phase of cyclosporin treatment, there was no difference in renal plasma flow and glomerular filtration rate between patients with or without lacidipine.

Following the oral administration of 4 mg lacidipine to volunteer subjects, a minimal prolongation of QTc interval has been observed (mean QTcF increase between 3.44 and 9.60 ms in young and elderly volunteers).
This was not associated with any adverse clinical effects or cardiac arrhythmias on monitoring.

5.2 Pharmacokinetic properties

Absorption

Lacidipine is a highly lipophilic compound; it is rapidly absorbed from the gastrointestinal tract following oral dosing.

Absolute bioavailability averages about 10% due to extensive first-pass metabolism in the liver.

Peak plasma concentrations are reached between 30 and 150 minutes.

Elimination

The drug is eliminated primarily by hepatic metabolism (involving cytochrome P450 CYP3A4). There is no evidence that lacidipine causes either induction or inhibition of hepatic enzymes.

The principal metabolites possess little, if any, pharmacodynamic activity.

Approximately 70% of the administered dose is eliminated as metabolites in the faeces and the remainder as metabolites in the urine.

The average terminal half-life of lacidipine ranges from between 13 and 19 hours at steady state.

5.3 Preclinical safety data

The only significant toxicological findings with lacidipine were reversible and consistent with the known pharmacological effects of calcium antagonists at high doses – decreased myocardial contractility and gingival hyperplasia in rats and dogs and constipation in rats.

In rats treated at high doses (15mg/kg bw with a NOAEL of 2.5 mg/kg bw) up to Day 14 of gestation, intra-uterine deaths occurred and placental weights were increased. In rabbits treated at high doses (18mg/kg bw with a NOAEL of 9 mg/kg bw) between days 6 and 18 of gestation, there was a reduction in fetal weights. In rats treated before littering and during lactation, there was a reduction in body weight gain of the offspring from day 7 post partum up to weaning with concomitant effects on physical development.
In rats at high doses, an inhibitory action on intense uterine contractions was observed.
Lacidipine has no genotoxic potential in a battery of *in vitro* and *in vivo* tests.
There was no evidence of carcinogenicity in mice. As with other calcium channel antagonists, a carcinogenicity study has shown an increase in benign interstitial cell tumors in rat testes.
The endocrine mechanisms believed to be involved in the production of interstitial hyperplasia and adenomas in rats are not relevant to humans

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
Povidone K 30

Lactose monohydrate
Magnesium stearate

Film-coating Opadry OY-S-7335:
Titanium dioxide
Hypromellose

6.2 Incompatibilities
Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

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

6.5 Nature and contents of container
Lacidipine 4 mg film-coated tablets are packaged in Aluminium/Aluminium blisters placed into cardboard boxes containing 14, 28, 30 or 90 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER

Rivopharm UK Ltd.
100 Bishopsgate
London
EC2N 4AG
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 33155/0021

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 DATE OF REVISION OF THE TEXT

24/08/2023