1. Name of the medicinal product

Lofral™ 5 mg *tablets*

Lofral™ 10 mg *tablets*

2. Qualitative and quantitative composition

1 Lofral 5 tablet contains: 5 mg amlodipine as 6.94 mg amlodipine besilate.

1 Lofral 10 tablet contains: 10 mg amlodipine as 13.89 mg amlodipine besilate.

3. Pharmaceutical form and amount of active substance per unit

Lofral™ 5 mg *tablets.* Pack of 30 tablets

Lofral™ 10 mg *tablets***.** Pack of 30 tablets

4. Clinical particulars:

1. Arterial hypertension: Lofral is indicated for the basic treatment of hypertension. Combination therapy may be of advantage in patients who have insufficiently responded to monotherapy. Lofral has been used together with thiazide diuretics, with alpha-blockers, with beta-blockers and with ACE inhibitors.
2. Prophylaxis of attacks in stable angina pectoris which is caused by fixed vasoconstriction.
3. Prinzmetal's or vasospastic angina which is caused by coronary vasospasm.

Lofral may be used in those cases where the clinical picture suggests a vasospasm component but this has not been confirmed. Lofral may be administered as monotherapy or in combination with other anti-anginal medicinal products in patients whose angina pectoris does not sufficiently respond to nitrates and/or adequate doses of beta-blockers.

N.B.: Lofral is not suitable for treating an acute attack of angina pectoris (attack suppression) because of its slow onset of action.

4.2 Posology/Administration

For both indications – hypertension and angina pectoris – treatment is usually started with a dose of 5 mg Lofral once daily. Depending on the individual response of the patient, the dose may be increased to 10 mg Lofral once daily.

An adjustment in the dose of Lofral is not necessary when co-administered with thiazide diuretics, beta-blockers or ACE inhibitors.

Special dosage instructions

Elderly patients

Peak plasma concentrations of amlodipine are attained almost at the same time in elderly and young individuals alike.

In elderly patients, amlodipine clearance is reduced, which leads on average to an increase in the AUC (area under the concentration-time curve) by about 50% and to an increase in the terminal elimination half-life.

The increase in AUC and the prolongation of the terminal elimination half-life in patients with heart failure were as expected for patients in the age group investigated. At comparable doses, amlodipine is equally well tolerated by elderly and young patients.

A lower initial dose may therefore be necessary in elderly patients.

Children

Children and adolescents with hypertension from 6 years to 17 years of age:
The recommended antihypertensive oral dose in paediatric patients ages 6-17 years is 2.5 mg once daily as a starting dose, up-titrated to 5 mg once daily if blood pressure
goal is not achieved after 4 weeks. Doses in excess of 5 mg daily have not been studied in paediatric patients. For children under 6 years old, no data are available."

under 18 years of age.

Renal insufficiency

In cases of renal insufficiency, Lofral is extensively metabolised to inactive metabolites, and only 10% of the medicinal product is excreted unchanged in the urine. Fluctuations in the plasma amlodipine concentration are not correlated with the degree of renal impairment. Lofral can therefore be administered in normal doses to patients with renal failure. Lofral is not dialysable.

Hepatic insufficiency

As with all calcium antagonists, the half-life of Lofral is prolonged in hepatic insufficiency. Since there are no dose recommendations for these patients, Lofral should be used with caution in hepatic insufficiency.

4.3 Contraindications

Hypersensitivity to the active substance, dihydropyridines (amlodipine is a dihydropyridine derivative) or to any of the excipients listed in the composition.

"severe hypotension
- shock (including cardiogenic shock)
- obstruction of the outflow tract of the left ventricle (e.g. high grade aortic stenosis)
- haemodynamically unstable heart failure after acute myocardial infarction"

4.4 Special Warnings and precautions for use

Clinical data available to date regarding administration of Lofral to patients less than 18 years of age are insufficient.

As with all calcium antagonists, the half-life of Lofral is prolonged in patients with hepatic insufficiency. Since there are no dose recommendations for these patients, Lofral should be used with caution in hepatic insufficiency.

Short-acting calcium antagonists of the 1,4-dihydropyridine type with a rapid onset of action are contraindicated in acute myocardial infarction and in the subsequent 30 days as a result of increased mortality. Whether this also applies to treatment with long-acting dihydropyridines with a prolonged onset of action is questionable on the basis of the data currently available. During this period, therefore, the physician should decide on the start of therapy and should monitor patients with particular care at the start of treatment.

Use in patients with heart failure

In a long-term, placebo-controlled study in patients with NYHA classes III and IV heart failure (without clinical symptoms or objective findings that would indicate an underlying ischaemic disorder), amlodipine had no effect on overall mortality or cardiovascular mortality when administered with stable doses of ACE inhibitors, digitalis and diuretics. Pulmonary oedema occurred significantly more frequently in the same population on amlodipine, although there was no significant difference in the incidence of worsening heart failure compared with placebo.

4.5 Interactions with other medicinal products and other forms of interaction

Other antihypertensives: Lofral may be administered together with thiazide diuretics, alpha-blockers, beta-blockers, ACE inhibitors, long-acting nitrates, sublingual nitroglycerine, non-steroidal anti-inflammatory drugs, antibiotics and oral antidiabetics.

Combination treatment may lead to a pronounced decrease in blood pressure due to the synergistic effect of amlodipine and other antihypertensives.

Theophylline, ergotamine: Calcium antagonists can interfere with the cytochrome P450-dependent metabolism of theophylline and ergotamine. Since neither *in vitro* nor *in vivo* interaction studies have been performed to date with theophylline or ergotamine and amlodipine, it is recommended that the blood concentrations of theophylline or ergotamine be regularly monitored at the start of co-administration.

Simvastatin: Repeated use of 10 mg amlodipine in combination with 80 mg simvastatin, compared to simvastatin alone, led to a 77% increase in plasma simvastatin levels. In patients receiving amlodipine, the dose of simvastatin should be limited to 20 mg per day.

Grapefruit (juice): The use of amlodipine with grapefruit or grapefruit juice is generally not recommended, as this may increase the bioavailability of amlodipine in some patients and thereby enhance the antihypertensive effect. The reason may be a genetic polymorphism of CYP34A, the principal enzyme responsible for the metabolism of amlodipine. A study in 20 healthy volunteers did not find any significant effect of grapefruit juice on the pharmacokinetics of amlodipine.

Special studies: Effects of other active substances on amlodipine

Cimetidine: Combined administration of amlodipine and cimetidine does not alter the pharmacokinetics of amlodipine.

Aluminium/magnesium (antacids): Co-administration of aluminium/magnesium antacids with a single dose of amlodipine had no significant effect on the pharmacokinetics of amlodipine.

Sildenafil: A single dose of sildenafil (100 mg) administered to patients with essential hypertension had no effect on the pharmacokinetic parameters of amlodipine. When amlodipine and sildenafil were administered in combination, each active substance independently exerted its hypotensive effect.

CYP3A4 inhibitors: Co-administration of 180 mg diltiazem per day and 5 mg amlodipine in elderly hypertensive patients (69 to 87 years of age) led to a 57% increase in the systemic availability of amlodipine. Co-administration of erythromycin in healthy volunteers (18 to 43 years of age) did not significantly alter the systemic availability of amlodipine (increase in the AUC by 22%). Potent CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, ritonavir) may increase the plasma levels of amlodipine to a greater extent than diltiazem. The clinical relevance of the above-mentioned observations is unclear. However, amlodipine should be used with particular caution in combination with CYP3A4 inhibitors, especially in elderly patients.

Clarithromycin: As clarithromycin is a CYP3A4 inhibitor, there is an increased risk of hypotension in patients receiving clarithromycin together with amlodipine. Close patient observation is indicated when amlodipine and clarithromycin are co-administered.

CYP3A4 inducers: There are no available data on the effect of CYP3A4 inducers on amlodipine. Combined use of CYP3A4 inducers (e.g. rifampicin, St. John's wort [*Hypericum perforatum*]) might lead to reduced plasma levels of amlodipine. Amlodipine should therefore be used with caution if co-administered with CYP3A4 inducers.

Special studies: Effects of amlodipine on other active substances

Atorvastatin: Co-administration of multiple doses of amlodipine (10 mg) with atorvastatin (80 mg) resulted in no significant changes in the steady-state pharmacokinetic parameters of atorvastatin.

Digoxin: Studies in healthy volunteers have shown that co-administration of amlodipine with digoxin does not produce any changes in the plasma digoxin level, or in renal digoxin clearance.

Ethanol (alcohol): Single and multiple doses of amlodipine (10 mg) had no significant effect on the pharmacokinetics of ethanol.

Warfarin: Co-administration of amlodipine and warfarin did not significantly alter the effect of warfarin on the prothrombin time in healthy male subjects.

Ciclosporin: No interaction studies of ciclosporin and amlodipine in healthy subjects and in other populations, with the exception of renal transplant patients, have been performed. Various studies in

renal transplant patients have shown that co-administration of ciclosporin and amlodipine has different effects on trough ciclosporin concentrations. The effect ranges from the absence of a change to a mean increase of 40%. Particular attention should be paid to ciclosporin levels in renal transplant patients receiving amlodipine.

Tacrolimus: With co-administration of amlodipine, there is an increased risk of elevated tacrolimus blood levels. To avoid the toxicity of tacrolimus when administering amlodipine in patients treated with tacrolimus, tacrolimus blood levels must be monitored and the tacrolimus dose adjusted if required.

Other: *In vitro* studies with human plasma show that amlodipine has no effect on protein binding of digoxin, phenytoin, coumarin, warfarin or indometacin.

4.6 Fertility, Pregnancy and lactation

In animal studies, rats treated with amlodipine (at 50 times the maximum recommended human dose) showed delayed onset of parturition and prolonged duration of labour. To date, however, no studies are available on the safe use of Lofral in pregnant and breast-feeding women. Lofral must not be used during pregnancy unless it is absolutely necessary. The fertility of rats was not affected by amlodipine treatment (see "Preclinical safety data – fertility disorders").

If Lofral is necessary during lactation, breast-feeding should be discontinued.

4.7 Effects on ability to drive and use machines

Owing to the possibility of undesirable effects, Lofral may impair responsiveness and the ability to drive and use tools and machines.

4.8 Undesirable effects

Amlodipine is well tolerated. Undesirable effects are arranged according to system organ class and frequency using the following definitions: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000).

Organ System	**Very common (≥ 1/10)**	**Common (≥ 1/100 to < 1 /10)**	**Uncommon (≥ 1/1,000 to 1/100);**	**Rare (≥ 1/10,000 to < 1/1,000)**	**Very rare (< 1/10,000)**
Blood and					leukopenia,

lymphatic system disorders					thrombocytopenia.
Immune system disorders					allergic reactions.
Metabolism and nutrition disorders					hyperglycaemia.
Psychiatric disorders			insomnia, mood changes.		
Nervous system disorders		dizziness, headache, somnolence.	tremor, taste disorders, syncope, hypoaesthesia, paraesthesia.		increased muscle tone, peripheral neuropathy. *Not known*: extrapyramidal disorder.
Eye disorders			visual disturbances. *Ear and labyrinth disorders*		
Ear Disorders			tinnitus.		
Cardiac disorders		palpitations.			myocardial infarction, arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation), which, however, cannot be

					differentiated from the natural course of the underlying disease.
Vascular disorders		facial flushing.	hypotension		vasculitis.
Respiratory, thoracic and mediastinal disorders			dyspnoea, rhinitis.		cough
Gastrointestinal disorders		abdominal pain, nausea.	vomiting, dyspepsia, change in bowel habits, dry mouth.		pancreatitis, gastritis, gingival hyperplasia.
Hepatobiliary disorders					epatitis, jaundice, elevated liver enzymes (usually accompanied by cholestasis).
Skin disorders			Very rare: angioedema, erythema multiforme, urticaria, exfoliative dermatitis,		
Musculoskeletal disorders			arthralgia, myalgia, muscle cramps, back pain		
Renal and urinary disorders			micturition disorders, nocturia,		

			pollakiuria.		
Reproductive system and breast disorders			erectile dysfunction, gynaecomastia.		
General disorders	oedema (11.1%)	fatigue	asthenia, pain, malaise, chest pain		
Investigations			weight gain, weight loss		

To report any side effect(s):

- **Saudi Arabia**

The National Pharmacovigilance and Drug Safety Centre (NPC)

- Fax: +966-11-205-7662
- Call NPC at +966-11-2038222, Exts: 2317-2356-2353-2354-2334-2340
- Toll free phone: 8002490000
- E-mail: npc.drug@sfda.gov.sa
- Website: www.sfda.gov.sa/npc

4.9 Overdose

Available data indicate that a severe overdose can lead to marked peripheral vasodilation and possibly reflex tachycardia. Significant and prolonged systemic hypotension as far as shock with a fatal outcome has been described.

Absorption of amlodipine was significantly reduced by the administration of activated charcoal to healthy volunteers immediately or up to two hours after ingestion of 10 mg amlodipine.

Gastric lavage may be helpful in some cases and is recommended as one of the usual safety precautions.

Clinically relevant hypotension resulting from an Lofral overdose calls for immediate action to support the cardiovascular system: frequent monitoring of cardiac and respiratory function, circulating volume and renal excretion, as well as elevation of the lower extremities. The administration of vasoconstrictive agents can be helpful in supporting vascular tone and blood pressure, provided that vasoconstrictors are not contraindicated. Intravenous calcium gluconate can be helpful for reversing the effect of calcium antagonists.

Since Lofral is highly bound to proteins, dialysis can probably not be expected to be of benefit.

5.0 Pharmacological properties:

5.1 Pharmacodynamic properties

ATC code: C08CA01

Mechanism of action/Experimental findings (in vitro)

Lofral prevents transmembrane influx of calcium ions into myocardial cells and vascular smooth muscle cells, i.e. Lofral is a slow channel blocker and acts as a calcium antagonist.
The antihypertensive effect of Lofral is based on a direct relaxant effect on the vascular smooth muscle cells.

Clinical efficacy

In patients with hypertension, a once-daily dose leads to a clinically significant lowering of blood pressure in both the supine and standing position for 24 h. The onset of effect is slow.

Experimental findings

The precise mechanism of the anti-ischaemic effect is not yet fully elucidated. It is known that Lofral prevents attacks of angina pectoris in the following two ways:

1. Amlodipine dilates peripheral arterioles and in this way reduces total peripheral resistance ("afterload"), against which the heart works. Since the heart rate remains stable, this decrease in the load reduces myocardial energy consumption and oxygen demand.

2. The mechanism of action of Lofral probably includes dilation of the major coronary vessels and coronary arterioles, in both healthy and ischaemic areas. This vasodilation improves the oxygen supply to the myocardium in patients with coronary artery spasms (Prinzmetal's or vasospastic angina) and reduces coronary vasoconstriction caused by smoking.

In patients with angina, a single daily dose of amlodipine increases total exercise time and prolongs the time to onset of an attack and the time to 1 mm ST segment depression. It also reduces the frequency of attacks and the need for nitroglycerine.

Use in patients with heart failure

Haemodynamic studies and exercise-based controlled clinical studies in NYHA class II to IV heart failure patients have shown that amlodipine does not lead to clinical deterioration as measured by exercise tolerance, left-ventricular ejection fraction and clinical symptoms (see also "Special warnings and precautions for use").

5.2 Pharmacokinetic properties

Independently of food intake, amlodipine is well absorbed after oral administration of therapeutic doses, attaining peak plasma concentrations after 6 to 12 hours. The volume of distribution is

approximately 21 l/kg. The terminal plasma half-life is 35-50 hours and permits once-daily dosing. The steady-state concentration is attained after 7-8 days of administration.

Amlodipine metabolism is mainly mediated by cytochrome P450 (CYP) 3A4 isoenzymes (major pathway). Amlodipine clearance is low and no clinically relevant interactions have been demonstrated with moderate CYP3A4 inhibitors (diltiazem) or substances that induce metabolism via CYP3A4. No interaction studies with more potent CYP3A4 inhibitors (e.g. ketoconazole, itraconazole or ritonavir) or CYP3A4 inducers (e.g. rifampicin) have been performed.

Amlodipine is largely metabolised to inactive metabolites. In the urine, 10% of the substance is excreted in unchanged form and 60% in the form of metabolites.

In vitro studies have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins.

In healthy subjects, amlodipine did not significantly influence the effect of co-administered warfarin on the prothrombin time. It can therefore be expected that existing warfarin treatment requires no modification as a result of adding amlodipine.

Absolute bioavailability in humans is 64-80%.

Use in elderly patients

The time to peak plasma concentrations is the same in elderly and young patients. In elderly patients, amlodipine clearance seems to be reduced, leading to an increase in AUC and elimination half-life. The increase in AUC and elimination half-life in patients with chronic heart failure matched expectations with regard to the age group studied (see also “Special warnings and precautions for use”).

5.3 Preclinical safety data

Carcinogenicity

Rats and mice treated with amlodipine in the diet for up to two years at concentrations calculated to provide daily dose levels of 0.5, 1.25 and 2.5 mg/kg/day showed no signs of carcinogenicity. The maximum dose (for mice similar to, and for rats double*, the maximum recommended clinical dose of 10 mg based on mg/m²) was near to the maximum tolerance dose for mice, but not for rats.

Mutagenicity

Mutagenicity studies have shown no active substance-related effects either at a gene or chromosome level.

Fertility disorders

The fertility of rats was not affected by amlodipine treatment (males treated for 64 days and females treated for 14 days before mating) at doses of up to 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg based on mg/m²).

* Based on a patient weighing 50 kg.

6.0 Pharmaceutical particulars

6.1 List of excipients

Cellulose microcrystalline, Calcium hydrogen phosphate,
Anhydrous, Sodium starch glycollate, type A, Magnesium stearate.

6.2 Incompatibilities

Effect on diagnostic methods

No known effects.

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store in the original package out of the reach and sight of children.

Climatic zone I and II: Do not store above 25°C.

Climatic zone III and IV: Do not store above 30°C.

Presentation

Lofral-5 mg tablets

White to off-white round tablets, with “A/5” embossed on break line side and “mp” on convex side.

Lofral-10 mg tablets

White to off-white round tablets, with “A/10” embossed on break line side and “mp” on convex side.

The tablets are packed in PVC/PVDC/Aluminium blisters.

Packs of 30 tablets.

6.6 Special precautions for disposal and other handling

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

7. Marketing authorisation holder

Acino Pharma AG, Liesberg, Switzerland

8.0 Marketing authorisation number

Lofral 5 mg Tablets; 23-222-07

Lofral 10 mg Tablets: 24-222-07

9. Date of first Authorisation

05 March 2007

10. Date of revision of the text

November 2014