LOFRAL™

LOFRAL™ -5 - tablets with amlodipine 5 mg
LOFRAL ™ -10 - tablets with amlodipine 10 mg

Qualitative and quantitative composition

LOFRAL ™-5 - tablets with 5 mg
Amlodipine besylate ..... 6,944 mg
(⇔ 5 mg amlodipine base)
Microcrystallin Cellulose ..... 124,056 mg
Anhydrous dibasic calcium phosphate..... 63,000 mg
Sodium starch glycolate ..... 4,000 mg
Magnesium stearate..... 2,000 mg

Packages with 10, 30 and 60 tablets of Amlodipine with 5 mg of Amlodipine base.

LOFRAL ™ -10 - tablets with 10 mg
Amlodipine besylate ..... 13,886 mg
(⇔ 10 mg amlodipine base)

Microcrystalline Cellulose ..... 248,111 mg
Anhydrous dibasic calcium phosphate ..... 126,000 mg
Sodium starch glycolate ..... 8,000 mg
Magnesium stearate..... 4,000 mg

Packages with 10, 30 and 60 tablets of Amlodipine with 10 mg of Amlodipine base.

Pharmaceutical Form
Tablets for oral administration

Clinical Particulars

Therapeutic Indications
Lofral is indicated for treatment of:

Essential hypertension (in monotherapy and associated to thiazide diuretics or angiotensin converting enzyme inhibitors (ACEI))
Myocardium ischemia or angor (unstable angina and vasospasm angina or Prinzmetal) isolated or associated to other therapy

Posology and Method of Administration
Usual adult doses are 2,5 mg to 10 mg, once a day, and the maximum daily dose of 10 mg should not be over passed.

	Initial Doses	Maintenance Doses
HYPERTENSION	2,5 - 10 mg	5 - 10 mg
ANGINA PECTORIS	5 - 10 mg	10 mg

Adult initial dose is 5 mg, as a single daily dose and for hypertension control, in elderly and hepatic impairment is recommended 2,5 mg. This dose can be increased to 10 mg in intervals of 7 to 14 days (or shorter intervals, if necessary), in function of patient response.

Maintenance dose are 5 mg to 10 mg in hypertension and 10 mg for angina control.

Amlodipine association to thiazide diuretics (hydrochlorothiazide) ACE inhibitors (angiotensin converting enzyme) (e.g. Captopril, enalapril) and β-blockers (eg. Atenolol) does not need dose adjustments.

Contra-indications
Patients with known hypersensitivity to amlodipine or dihydropyridines, in general.

Warnings and special precautions for use
Caution is recommended in the followings conditions:

Patients with severe left ventricular dysfunction, especially in case of β-blocker combined therapy;
In elderly patients and hepatic impaired (see pharmacokinetic properties) a dose reduction should be considered, especially in what concerns initial dose; 2,5 mg to control hypertension and 5 mg for angina control;
In prolonged therapies is advisable to monitor hepatic function, in patients with compromised function;
A β-blocker sudden therapy interruption should be avoided before initiating amlodipine treatment;
Amlodipine treatment interruption should be gradual.

In patients with hypertrophic cardiomyopathy (especially obstructive), oedema and intracranial pressure increase should be used carefully.

Interaction with medicines and other forms of interactions
Amlodipine has been associated with therapeutic benefits to ACE inhibitors, thiazide diuretics and β-blockers.
Amlodipine does not alter digoxin plasma concentrations and no problems were registrated when it was administrated simultaneously with cimetidine, warfarin, phenytoin and indomethacin. Food presence has no effect on amlodipine's absorption.

Interaction with CYP3A3/4 substrate-drugs
Effect increase; cyclosporine and amlodipine association causes cyclosporin, amlodipine and fentanyl concentrations increase, and severe hypotension can occur.

Pregnancy and lactation
Animal studies did not reveal teratogenic properties with a dose several times higher to maximum recommended therapeutic dose for Man.
With these dose rats females presented an increase in gestation time and delivery.

Nevertheless, because these are no controlled studies in pregnant women and also because animal studies are not always capable to extrapolation for human species, during pregnancy the medicine use is not advised, as well as during the lactation, except when the benefit risk relation is justified.

Effects on ability to drive and use machines
No effects interfering in both abilities are known.

Undesirable effects
Adverse reactions > 10 % :
- Cardiovascular: peripheral oedema.

Adverse reactions between 1 and 10 %:
- Cardiovascular: flushing, palpitations;
- Central nervous system: headache, fatigue, dizziness, somnolence (1-2 %);
- Dermatological: Dermatitis, rash (1-2 %), pruritus, urticaria (1-2 %);
- Endocrine, metabolic: sexual dysfunction (1-2 %);
- Neuromuscular and skeletal: cramps (1-2 %).

Adverse reactions < 1 % :
Hypotension, bradycardia, arrythmia, ECG alterations, ventricular extrasystoles, syncope, tachycardia, nervosity, psychiatric dysfunction, insomnia, alopecia, petechia, weight gain, anorexia, diarrhoea, constipation, vomiting, xerostomia, flatulence, joint alterations, weakness, paresthesia, tremors, nasal congestion, cough, epistaxis, diaphoresis.

Overdose
There are no known documented cases of amlopidine overdose, but due its vasodilator properties, supposedly massive ingestion leads to an important peripheral vasodilation with accentuated and prolonged systemic hypotension.

Measures to be adopted include general support measures with cardiovascular and respiratory function monitoring. A vasoconstrictor administration is indicated in order to re-establish vascular tonus and blood pressure.

Gastric emptying can be advantageous due to amlodipine slow oral absorption (plasma peaks at 6-9 hours), but dialysis has no effect.

Pharmacological properties

Pharmacodynamic properties
Amlodipine is a calcium-channel antagonist, a basic dihydropyridine derivate, structurally related to nifedipine, differing from it by its higher oral bioavailability and prolonged half-life.

Amlodipine ionizes at physiologic pH and its calcium channels binding is increased to a lower pH, like the one occurring in ischemia conditions.

Amlodipine inhibits in a prolonged form the calcium entrance through the slow calcium channels, at smooth muscle cells and myocardium cells level.

The site of main action is peripheral, but it also produces coronary vascularization vasodilation.

Unlike other cardiovascular agents, amlodipine has no significant effect on sinoatrial and atrioventricular nodules and consequently does not alter cardiac conduction. Also, it has not been associated to metabolic adverse effects (it does not modify plasma lipids levels) and can be used in diabetics, asthmatics and hyperuricemia patients.

Short and mid-term clinical trials indicate that amlodipine is effective in angina pectoris (stable and variant) and in mild to moderate hypertension.

In hypertensive patients, a single daily dose, allows obtaining a significant reduction of pressure levels without increasing cardiac frequency. Amlodipine's progressive action and the absence of plasma concentration peaks avoids hypotensive crisis.

Amlodipine decreases total peripheral resistances (post-charge) without inducing reflex tachycardia. This action is accompanied by myocardium energy consumption decrease, coronary arteries and arterioles vasodilation, resulting in an increase of coronary blood flow and oxygen needs reduction.

In angor patients, amlodipine administration, in a single daily dose, increases the effort duration and reduces the angor crisis frequency and intensity, as well as nitroglycerin necessity.

In the animal, amlodipine demonstrated natriuretic and diuretic effects, as well as evidences of a potential cardioprotection and anti-atherosclerotic effect.

Pharmacokinetic properties
After oral administration of therapeutic dose, amlodipine is slowly and almost completely absorbed; plasma concentration peaks are reached 6 to 9 hours after administration. Absolute bioavailability is 60-65 % and is not influenced by food.

Amlodipine has a lineal pharmacokinetic profile with good correlation between oral dose and Cmax. Plasma steady-state levels are reached after 7 to 8 hours consecutive daily administrations, without accumulation evidences.

Volume of distribution is high (21 l/kg): Plasma proteins binding is around 98 % and terminal plasma half-life is 30-45 hours. Amlodipine undergoes an extended hepatic metabolization; inactive metabolites are mostly excreted in urine (60 %) and the unalterated fraction is 5-10 %.

In elderly patients, amlodipine plasma concentrations are higher than in young adults. Nevertheless, terminal elimination half-lives are identical for both age groups.

In renal impaired patients there is no correlation between amlodipine plasma concentrations and renal compromise degree.

Preclinical safety data
Amlodipine LD50 in rats is, oral route, 393 mg/kg for males and 686 mg/kg for females. Dose up 30 mg/kg/day, during three months, did not cause death in rats and in an one year trial the dose 2 mg/kg/day was found "no effect".

Pharmaceutical particulars

List of excipients
Microcrystalline cellulose, anhydrous dibasic calcium phosphate, sodium starch glycolate and magnesium stearate.

Incompabilities
None to this date

Special precautions for storage

Do not store above 25°C
Keep out of the reach and sight of children.
Do not use this medication after the expiry date stated "EXP" on the packaging.

Nature and content of the container
Blisters thermo-sealed light-proof made of PVC/ PVDC foil with width of 0,25 mm and aluminium foil with width of 0,02 mm.

Presentation in packages with 10, 30 and 60 divisible tablets of LOFRAL™ - 5
and packages with 30 and 60 divisible tablets of LOFRAL™ - 10.

Instructions for use/handling
Take the tablet out of the blister and swallow it with water.
Keep the package away from heat and moisture.

Presentation
Lofral 5 mg tablet:
Packings of 10 and 30 tablets

Lofral 10 mg tablet:
Packings of 10 and 30 tablets

Date of information

February 2000

THIS IS A MEDICAMENT

Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.

- The doctor and the pharmacist are the experts in medicines, their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.
-Keep all medicaments out of reach of children.

Council of Arab Health Ministers,
Union of Arab Pharmacists.

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