Client		Color :	Finishing :
Product	**Dirslip ACTAPIN MY**	**BLACK**	**TIDAK DILIPAT**
Dimension	**146 x 248mm**		
Code	**41605-03**		
Material	**HVS 70gr**		
Date			

Actapin
Amlodipine

Description
Actapin 5 mg Tablet : White, round, at, 8 mm tablets with score on one side and code "AB5" on the other side
Actapin 10 mg Tablet : White, round, at, 10 mm tablets with score on one side and code "AB10" on the other side

Pharmacological Properties
Pharmacodynamic properties
Dihydropyridine derivative with long half-life. Eases cardiac work and lowers peripheral resistance. No effect on supraventricular arrhythmias.
Mechanism of action:
Inhibits calcium ion influx in cardiac muscle cells and vascular smooth muscle.
Pharmacodynamic effects:
Vasodilatation with reduction of peripheral vessel resistance reduces afterload and lowers raised blood pressure. As the heart rate is unaffected, reduction of cardiac works reduces cardiac energy consumption and oxygen need. This, and dilatation of the coronary vessels, explains the effect of amlodipine in angina pectoris.
In patients with hypertension, a once daily dose gives a clinically significant reduction of both supine and standing blood pressure over 24 hours. Due to slow initial effect, there is little danger of acute hypotension.
Taken daily by patients with angina pectoris, amlodipine increases total exercise capacity, and increases the time to an anginal attack and to 1 mm ST segment depression. Frequency of anginal attacks and use of nitroglycerine are reduced.
Amlodipine has not been shown to cause metabolic side effects or changes in plasma lipids. It may be used by patients with asthma, diabetes and gout. In cardiac failure patients with NYHA classes II-IV, amlodipine has not been shown to cause clinical deterioration as measured by exercise tolerance, left ventricular ejection fraction and clinical symptomatology. In patients with NYHA classes III-IV, treated with digitalis, diuretics and ACE inhibitors, amlodipine has not been shown to lead to an increased risk of mortality or morbidity, but it associated with increased incidence of pulmonary oedema.

Pharmacokinetic properties
Absorption:
Peak plasma concentration is reached after 6 - 12 hours. Bioavailability is 64 - 80%.
Distribution:
The distribution volume is approx. 21 l/kg. Protein binding is approx. 97.5% in vitro.
Biotransformation:
Mainly metabolized to inactive metabolites in the liver.
Elimination:
The half-life is 35-50 hours. Effective plasma concentration are maintained for 24 hours with one dose daily. Steady state is reached after 7 - 8 days. 10% is excreted unchanged and 60% as metabolites in the urine.
Use in elderly patients
Time to peak plasma concentration of amlodipine is the same in younger and elderly patients. Amlodipine clearance tends to be reduced, with a resulting increase in AUC and half-life in elderly patients. An increase in AUC and half-life in patients with cardiac failure is as expected considering the patients age.

Indications
- Hypertension.
- Chronic Stable angina and/or Prinzmetal/variant angina.

Posology
Posology and method of administration
The usual starting dose is 5 mg daily. May if necessary be increased to 10 mg daily. It is not necessary to adjust the dose of amlodipine during co-administration of thiazides, beta-blockers or ACE inhibitors (angiotensin-converting enzymes). Normal dosage regimens are recommended. Amlodipine, used at similar doses in elderly and younger patients, is equally well tolerated.
The efficacy and safety in children has not been investigated.

Contraindications
Hypersensitivity to dihydropyridines (amlodipine, nifedipine, felodipine, isradipine) or any of the excipients.
Pregnancy (see Pregnancy and lactation)
Severe hypertension.

Drug Interaction
Amlodipine has been safely administered with thiazide diuretics, alpha-blockers, beta-blockers, ACE inhibitors, long-acting nitrates, sublingual nitroglycerine, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.
In vitro data from studies with human plasma indicate that amlodipine has no effect on protein binding of the drugs tested (digoxin, phenytoin, warfarin, or indomethacin).

Simvastatin
Co-administration of multiple doses of 10 mg amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily.

Grapefruit Juice
Co-administration of 240 mL grapefruit juice with a single oral dose of 10 mg amlodipine in 20 healthy volunteers had no significant effect on the pharmacokinetics of amlodipine.
The study did not allow examination of the effect of genetic polymorphism in CYP3A4, the primary enzyme responsible for metabolism of amlodipine; therefore, administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients, resulting in increased blood pressure lowering effects.

CYP3A4 Inhibitors
Co-administration of a 180 mg daily dose of diltiazem with 5 mg amlodipine in elderly hypertensive patients (69 to 87 years of age) resulted in a 57% increase in amlodipine systemic exposure.
Co-administration of erythromycin in healthy volunteers (18 to 43 years of age) did not significantly change amlodipine systemic exposure (22% increase in area under the concentration versus time curve [AUC]).
Although the clinical relevance of these findings is uncertain, pharmacokinetic variations may be more pronounced in the elderly.
Strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of amlodipine to a greater extent than diltiazem. Amlodipine should be used with caution when administered with CYP3A4 inhibitors.

Clarithromycin
Clarithromycin is an inhibitor of CYP3A4. There is an increased risk of hypotension in patients receiving clarithromycin with amlodipine. Close observation of patients is recommended when amlodipine is co-administered with clarithromycin.

CYP3A4 Inducers
There is no data available regarding the effect of CYP3A4 inducers on amlodipine. Concomitant use of CYP3A4 inducers (e.g., rifampicin, hypericum perforatum) may decrease the plasma concentrations of amlodipine. Amlodipine should be used with caution when administered with CYP3A4 inducers.

In the following studies, there were no significant changes in the pharmacokinetics of either amlodipine or another drug within the study, when co-administered.

Special Studies: Effect of Other Agents on Amlodipine
Cimetidine
Co-administration of amlodipine with cimetidine did not alter the pharmacokinetics of amlodipine.

Aluminum/Magnesium (Antacid)
Co-administration of aluminum/magnesium (antacid) with a single dose of amlodipine had no significant effect on the pharmacokinetics of amlodipine.

Sildenafil
A single 100 mg dose of sildenafil in subjects with essential hypertension had no effect on the pharmacokinetic parameters of amlodipine. When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

Special Studies: Effect of Amlodipine on Other Agents
Atorvastatin
Co-administration of multiple 10 mg doses of amlodipine with 80 mg atorvastatin resulted in no significant change in the steady-state pharmacokinetic parameters of atorvastatin.

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Digoxin
Co-administration of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in healthy volunteers.

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

Warfarin
Co-administration of amlodipine with warfarin did not change the warfarin prothrombin response time.

Cyclosporin
No drug interaction studies have been conducted with cyclosporin and amlodipine in healthy volunteers or other populations, with the exception of renal transplant patients. Various studies in renal transplant patients report that co-administration of amlodipine with cyclosporine affects the trough concentrations of cyclosporin, from no change up to an average increase of 40%. Consideration should be given for monitoring cyclosporin levels in renal transplant patients on amlodipine.

Tacrolimus
There is a risk of increased tacrolimus blood levels when co-administered with amlodipine. In order to avoid toxicity of tacrolimus, administration of amlodipine in a patient treated with tacrolimus requires monitoring of tacrolimus blood levels and dose adjustment of tacrolimus when appropriate.

Mechanistic Target of Rapamycin (mTOR) Inhibitors
mTOR inhibitors such as sirolimus, temsirolimus, and everolimus are CYP3A substrates. Amlodipine is a weak CYP3A inhibitor. With concomitant use of mTOR inhibitors, amlodipine may increase exposure of mTOR inhibitors.

Warnings and Precautions
- Caution is recommended with high doses in elderly patients, as clearance appears to be reduced, resulting in higher plasma concentrations. The half-life is prolonged in patients with hepatic impairment and the preparation must therefore be used with caution in these patients.
- Use in patients with impaired liver function :
As with all calcium antagonists, amlodipine half-life is prolonged in patients with impaired liver function and dosage recommendations have not been established. The drug should therefore be administered with caution in these patients.
- Use in patients with impaired renal function :
Amlodipine is extensively metabolized to inactive metabolites with 10% excreted as unchanged drug in the urine. Amlodipine may be used in such patients at normal doses. Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment. Amlodipine is not dialyzable.

Patients with heart failure:
An association between amlodipine and increased incidence of pulmonary oedema has been seen in patients with NYHA III and IV heart failure of non-ischemic etiology (see pharmacodynamic properties).

Interaction with other medicinal products and other forms of interaction
See Drug Interaction

Pregnancy and lactation
Pregnancy
See Contraindications

Pharmacodynamic effects associated with hypotension in the mother way lead to foetal hypoxia. In high perinatal doses prolonged birth time and an increased rate of stillbirths have been observed in rats.

Lactation
It is not known whether breastfed children can be harmful affected. The preparation should therefore not be used during lactation.

Effects on ability to drive and use machines
Amlodipine is normally considered to have no or insignificant effects on the ability to drive or operate machinery.

Undesirable Effects
Amlodipine is usually well tolerated. In placebo-controlled studies in patients with hypertension or angina the commonest adverse reactions were :
Neurological reactions : Dizziness, headache, facial redness, flushing, somnolence.
General reactions : Muscle fatigue.
Cardiovascular reactions : Peripheral oedema (mainly of the ankles), palpitations.
Gastrointestinal reactions : Abdominal pain, nausea
Psychiatric reactions : Drowsiness

Less common adverse reactions seen after marketing were :
Neurological reactions : hypertonia, hypoesthesia/ paraesthesia, peripheral neuropathy, tremor, dry mouth.
General reactions : asthenia, back pain, malaise, pain, weight gain/loss.
Cardiovascular reactions : hypotension, syncope, vasculitis.
Endocrinal reactions : gynecomastia, increased sweating
Gastrointestinal reactions : altered bowel habit, dyspepsia (including gastritis), gingival hyperplasia, pancreatitis, vomiting.
Metabolic and nutritional disorders : hyperglycemia.
Reactions in muscles, connective tissue and skeleton : arthralgia, muscle cramps, myalgia
Reactions in the blood and lymph system : purpura, thrombocytopenia, leucopenia.
Psychiatric reactions : impotence, insomnia, mood changes
Respiratory reactions : cough, dyspnoea, rhinitis
Reactions in skin and subcutaneous tissue : alopecia, skin discolouration, urticaria
Special senses : taste changes
Reactions in the ear and labyrinth : tinnitus
Eye reactions : visual disturbances
Reactions in the kidney and urinary track : increased urinary frequency, micturition disorder, nocturia

Rare allergic reactions including pruritus, rash, angiooedema and erythema multiforme. Hepatitis jaundice, and raised liver enzymes have also been reported in rare cases (usually with cholestasis) occasionally serious enough to require hospitalization. In several cases the causal association with amlodipine was uncertain. Myocardial infarction, arrhythmias (including bradycardia, ventricular tachycardia and atrial fibrillation) and chest pain have been reported in rare cases, but a definite association with the treatment has not been established.

Overdose
Experience of overdose in human is limited. Gastric lavage may be effective in some cases. Patients with clinically significant hypotension should be monitored and given vasoconstrictors if necessary. As amlodipine is highly bound to plasma proteins, dialysis is not indicated.
Slow intravenous calcium may be useful in reversing the calcium entry blockade. Should be given as chloride, or if acidoses is present, as gluconate.

List of excipients:
Microcrystalline cellulose, dibasic calcium phospate anhydrous, sodium starch glycolate, magnesium stearate

ATC code : C08CA01

Storage
Do not store above 30°C

Presentation
Actapin 5 mg Tablets:
Available in box of 3 blisters x 10 tablets and 10 blisters x 10 tablets
Actapin 10 mg Tablets:
Available in box of 3 blisters x 10 tablets and 10 blisters x 10 tablets

This leaflet was last revised in May 2022

Manufactured by:
PT. Actavis Indonesia
Jl. Raya Bogor Km. 28, Kelurahan Pekayon, Kecamatan Pasar Rebo
Kota Jakarta Timur, Provinsi DKI Jakarta, Indonesia

Actavis