AMEDIN® TABLETS
Amlodipine
5mg and 10 mg

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

1. WHAT AMEDIN IS AND WHAT IT IS USED FOR
Amedin contains the active substance amlodipine which belongs to a group of medicines called calcium antagonists.
Amedin is used to treat high blood pressure (hypertension) or a certain type of chest pain called angina, a rare form of which is Prinzmetal's or variant angina.
In patients with high blood pressure this medicine works by relaxing blood vessels, so that blood passes through them more easily. In patients with angina Amedin works by improving blood supply to the heart muscle which then receives more oxygen and as a result chest pain is prevented. This medicine does not provide immediate relief of chest pain from angina.

2. WHAT YOU NEED TO KNOW BEFORE YOU TAKE AMEDIN
Contra-indications:
Do not take Amedin
- If you are allergic (hypersensitive) to amlodipine, or any of the other ingredients of this medicine, or to any other calcium antagonists. This may be itching, reddening of the skin or difficulty in breathing.
- If you have severe low blood pressure (hypotension).
- If you have narrowing of the aortic heart valve (aortic stenosis) or cardiogenic shock (a condition where your heart is unable to supply enough blood to the body).
- If you suffer from heart failure after a heart attack.

Appropriate precautions for use; special warnings; Warnings and precautions
Talk to your doctor or pharmacist before taking Amedin.
You should inform your doctor if you have or have had any of the following conditions:
- Recent heart attack
- Heart failure
- Severe increase in blood pressure (Hypertensive crisis)
- Liver disease
- You are elderly and your dose needs to be increased

Children and adolescents: Amedin has not been studied in children under the age of 6 years. Amedin should only be used for hypertension in children and adolescents from 6 years to 17 years of age. For more information, talk to your doctor.

Other medicines and Amedin: Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.
Amedin may affect or be affected by other medicines, such as:
- ketoconazole, itraconazole (anti-fungal medicines)
- ritonavir, indinavir, nelfinavir (so called protease inhibitors used to treat HIV)
- rifampicin, erythromycin, clarithromycin (antibiotics)
- hypericum perforatum (St. John's Wort)
- verapamil, diltiazem (heart medicines)
- dantrolene (infusion for severe body temperature abnormalities)
- tacrolimus, sirolimus, temsirolimus, and everolimus (medicine used to alter the way your immune system works)
- simvastatin (cholesterol lowering medicine)
- cyclosporine (an immunosuppressant)

Amedin may lower your blood pressure even more if you are already taking other medicines to treat your high blood pressure.

Amedin with food and drink: Grapefruit juice and grapefruit should not be consumed by people who are taking Amedin. This is because grapefruit and grapefruit juice can lead to an increase in the blood levels of the active ingredient amlodipine, which can cause an unpredictable increase in the blood pressure lowering effect of Amedin.

Pregnancy and breast-feeding
Pregnancy: The safety of amlodipine in human pregnancy has not been established. If you think you might be pregnant, or are planning to get pregnant, you must tell your doctor before you take Amedin.
Breast-feeding: Amlodipine has been shown to pass into breast milk in small amounts. If you are breast-feeding or about to start breast-feeding you must tell your doctor before taking Amedin.
Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines: Amedin may affect your ability to drive or use machines. If the tablets make you feel sick, dizzy or tired, or give you a headache, do not drive or use machines and contact your doctor immediately.

Amedin contains lactose: If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. HOW TO TAKE AMEDIN
Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.
The recommended initial dose is Amedin 5 mg once daily. The dose can be increased to Amedin 10 mg once daily.
This medicine can be used before or after food and drinks. You should take this medicine at the same time each day with a drink of water. Do not take Amedin with grapefruit juice.

Use in children and adolescents: For children and adolescents (6-17 years old), the recommended usual starting dose is 2.5 mg a day. The maximum recommended dose is 5 mg a day. Amedin 5 mg tablets can be divided into halves to provide a 2.5 mg dose. It is important to keep taking the tablets. Do not wait until your tablets are finished before seeing your doctor.

If you take more Amedin than you should: Taking too many tablets may cause your blood pressure to become low or even dangerously low. You may feel dizzy, lightheaded, faint or weak. If blood pressure drop is severe enough shock can occur. Your skin could feel cool and clammy and you could lose consciousness. Seek immediate medical attention if you take too many Amedin tablets.

If you forget to take Amedin: Do not worry. If you forget to take a tablet, leave out that dose completely. Take your next dose at the right time. Do not take a double dose to make up for a forgotten dose.

If you stop taking Amedin: Your doctor will advise you how long to take this medicine. Your condition may return if you stop using this medicine before you are advised.
If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS
Like all medicines, this medicine can cause side effects, although not everybody gets them. Visit your doctor immediately if you experience any of the following side effects after taking this medicine.
- Sudden wheeziness, chest pain, shortness of breath or difficulty in breathing
- Swelling of eyelids, face or lips
- Swelling of the tongue and throat which causes great difficulty breathing
  Severe skin reactions including intense skin rash, hives, reddening of the skin over your whole body, severe itching, blistering, peeling and swelling of the skin, inflammation of mucous membranes (Stevens Johnson Syndrome, toxic epidermal necrolysis) or other allergic reactions
- Heart attack, abnormal heart beat
- Inflamed pancreas which may cause severe abdominal and back pain accompanied with feeling very unwell

The following very common side effect has been reported. If this causes you problems or if it lasts for more than one week, you should contact your doctor.

Very common: may affect more than 1 in 10 people
- Oedema (fluid retention)

The following common side effects have been reported. If any of these cause you problems or if they last for more than one week, you should contact your doctor.

Common: may affect up to 1 in 10 people
- Headache, dizziness, sleepiness (especially at the beginning of treatment)
- Palpitations (awareness of your heart beat), flushing
- Abdominal pain, feeling sick (nausea)
- Altered bowel habits, diarrhoea, constipation, indigestion
- Tiredness, weakness
- Visual disturbances, double vision
- Muscle cramps
- Ankle swelling

Other side effects that have been reported include the following list. If any of these get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

Uncommon: may affect up to 1 in 100 people
- Mood changes, anxiety, depression, sleeplessness
- Trembling, taste abnormalities, fainting
- Numbness or tingling sensation in your limbs, loss of pain sensation
- Ringing in the ears
- Low blood pressure
- Sneezing/running nose caused by inflammation of the lining of the nose (rhinitis)
- Cough
- Dry mouth, vomiting (being sick)
- Hair loss, increased sweating, itchy skin, red patches on skin, skin discolouration
- Disorder in passing urine, increased need to urinate at night, increased number of times of passing urine
- Inability to obtain an erection, discomfort or enlargement of the breasts in men
- Pain, feeling unwell
- Joint or muscle pain, back pain
- Weight increase or decrease

Rare: may affect up to 1 in 1,000 people
- Confusion
- Very rare: may affect up to 1 in 10,000 people
- Decreased numbers of white blood cells, decrease in blood platelets which may result in unusual bruising or easy bleeding
- Excess sugar in blood (hyperglycaemia)
- A disorder of the nerves which can cause muscular weakness, tingling or numbness
- Swelling of the gums
- Abdominal bloating (gastritis)
- Abnormal liver function, inflammation of the liver (hepatitis), yellowing of the skin (jaundice), liver enzyme increase which may have an effect on some medical tests
- Increased muscle tension
- Inflammation of blood vessels, often with skin rash
- Sensitivity to light
- Disorders combining rigidity, tremor, and/or movement disorders

Reporting of side effects: If you get any side effects, talk to your doctor, your pharmacist or your nurse. This includes any possible side effects not listed in this leaflet. By reporting side effects you can help provide more information on the safety of this medicine.

5. CLINICAL PHARMACOLOGY
Pharmacodynamic properties
Pharmacotherapeutic group: Calcium channel blockers, selective calcium channel blockers with mainly vascular effects. ATC Code: C08CA01.
Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle.
The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle. The precise mechanism by which amlodipine relieves angina has not been fully determined but amlodipine reduces total ischaemic burden by the following two actions:
1) Amlodipine dilates peripheral arterioles and thus, reduces the total peripheral resistance (afterload) against which the heart works. Since the heart rate remains stable, this unloading of the heart reduces myocardial energy consumption and oxygen requirements.
2) The mechanism of action of amlodipine also probably involves dilatation of the main coronary arteries and coronary arterioles, both in normal and ischaemic regions. This dilatation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal's or variant angina).

In patients with hypertension, once daily dosing provides clinically significant reductions of blood pressure in both the supine and standing positions throughout the 24 hour interval. Due to the slow onset of action, acute hypotension is not a feature of amlodipine administration.

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In patients with angina, once daily administration of amlodipine increases total exercise time, time to angina onset, and time to 1 mm ST segment depression, and decreases both angina attack frequency and glyceryl trinitrate tablet consumption.
Amlodipine has not been associated with any adverse metabolic effects or changes in plasma lipids and is suitable for use in patients with asthma, diabetes, and gout.
Use in patients with coronary artery disease (CAD)
The effectiveness of amlodipine in preventing clinical events in patients with coronary artery disease (CAD) has been evaluated in an independent, multicentre, randomized, doubleblind, placebo-controlled study of 1997 patients;
Comparison of Amlodipine vs. Enalapril to Limit Occurrences of Thrombosis (CAMELOT). Of these patients, 663 were treated with amlodipine 5-10mg, 673 patients were treated with enalapril 10-20mg, and 655 patients were treated with placebo, in addition to standard care of statins, betablockers,diuretics and aspirin, for 2 years. The key efficacy results are presented in Table 1. The results indicate that amlodipine treatment was associated with fewer hospitalizations for angina and revascularization procedures in patients with CAD.

Table 1. Incidence of significant clinical outcomes for CAMELOT

	Cardiovascular event rates, No. (%)			Amlodipine vs. Placebo	
Outcomes	Amlodipine	Placebo	Enalapril	Hazard Ratio (95% CI)	P Value
Primary Endpoint					
Adverse cardiovascular events	110 (16.6)	151 (23.1)	136 (20.2)	0.69 (0,54-0,88)	.003
Individual Components					
Coronary revascularization	78 (11.8)	103 (15.7)	95 (14.1)	0.73 (0,54-0,98)	.03
Hospitalization for angina	51 (7.7)	84 (12.8)	86 (12.8)	0.58 (0,41-0,82)	.002
Nonfatal MI	14 (2.1)	19 (2.9)	11 (1.6)	0.73 (0,37-1,46)	.37
Stroke or TIA	6 (0.9)	12 (1.8)	8 (1.2)	0.50 (0,19-1,32)	.15
Cardiovascular death	5 (0.8)	2 (0.3)	5 (0.7)	2.46 (0,48-12,7)	.27
Hospitalization for CHF	3 (0.5)	5 (0.8)	4 (0.6)	0.59 (0,14-2,47)	.46
Resuscitated cardiac arrest	0	4 (0.6)	1 (0.1)	NA	.04
Newonset peripheral vascular disease	5 (0.8)	2 (0.3)	8 (1.2)	2.6 (0,50-13,4)	.24

Abbreviations: CHF, congestive heart failure; CI, confidence interval; MI, myocardial infarction; TIA, transient ischemic attack.

Use in patients with heart failure: Haemodynamic studies and exercise based controlled clinical trials in NYHA Class II-IV heart failure patients have shown that Amedin did not lead to clinical deterioration as measured by exercise tolerance, left ventricular ejection fraction and clinical symptomatology.
A placebo controlled study (PRAISE) designed to evaluate patients in NYHA Class III-IV heart failure receiving digoxin, diuretics and ACE inhibitors has shown that Amedin did not lead to an increase in risk of mortality or combined mortality and morbidity with heart failure.
In a followup, long term, placebo controlled study (PRAISE2) of Amedin in patients with NYHA III and IV heart failure without clinical symptoms or objective findings suggestive or underlying ischaemic disease, on stable doses of ACE inhibitors, digitalis, and diuretics, Amedin had no effect on total cardiovascular mortality. In this same population Amedin was associated with increased reports of pulmonary oedema.
Treatment to prevent heart attack trial (ALLHAT): A randomised double-blind morbidity-mortality study called the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was performed to compare newer drug therapies: amlodipine 2.5-10mg/d (calcium channel blocker) or lisinopril 1040 mg/d (ACEinhibitor) as firstline therapies to that of the thiazide-diuretic, chlorthalidone 12.5-25mg/d in mild to moderate hypertension.
A total of 33,357 hypertensive patients aged 55 or older were randomised and followed for a mean of 4.9 years. The patients had at least one additional CHD risk factor, including: previous myocardial infarction or stroke (> 6 months prior to enrollment) or documentation of other atherosclerotic CVD (overall 51.5%), type 2 diabetes (36.1%), HDLC < 35 mg/dL (11.6%), left ventricular hypertrophy diagnosed by electrocardiogram or echocardiography (20.9%), current cigarette smoking (21.9%).
The primary endpoint was a composite of fatal CHD or non-fatal myocardial infarction. There was no significant difference in the primary endpoint between amlodipine-based therapy and chlorthalidone-based therapy: RR 0.98 95% CI (0.90-1.07) p=0.65. Among secondary endpoints, the incidence of heart failure (component of a composite combined cardiovascular endpoint) was significantly higher in the amlodipine group as compared to the chlorthalidone group (10.2% vs. 7.7%, RR 1.38, 95% CI [1.25-1.52] p<0.001). However, there was no significant difference in all-cause mortality between amlodipine based therapy and chlorthalidone based therapy. RR 0.96 95% CI [0.891.02] p=0.20.
Use in children (aged 6 years and older): In a study involving 268 children aged 6-17years with predominantly secondary hypertension, comparison of a 2.5 mg dose, and 5.0 mg dose of amlodipine with placebo, showed that both doses reduced Systolic Blood Pressure significantly more than placebo. The difference between the two doses was not statistically significant.
The long-term effects of amlodipine on growth, puberty and general development have not been studied. The long-term efficacy of amlodipine on therapy in childhood to reduce cardiovascular morbidity and mortality in adulthood has also not been established.

Pharmacokinetic properties
Absorption, distribution, plasma protein binding: After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours post dose. Absolute bioavailability has been estimated to be between 64 and 80%. The volume of distribution is approximately 21 l/kg. In vitro studies have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins.
The bioavailability of amlodipine is not affected by food intake.
Biotransformation/elimination: The terminal plasma elimination half-life is about 35-50 hours and is consistent with once daily dosing. Amlodipine is extensively metabolised by the liver to inactive metabolites with 10% of the parent compound and 60% of metabolites excreted in the urine.
Hepatic impairment: Very limited clinical data are available regarding amlodipine administration in patients with hepatic impairment. Patients with hepatic insufficiency have decreased clearance of amlodipine resulting in a longer half-life and an increase in AUC of approximately 40-60%.
Elderly population: The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. Amlodipine clearance tends to be decreased with resulting increases in AUC and elimination half-life in elderly patients. Increases in AUC and elimination half-life in patients with congestive heart failure were as expected for the patient age group studied.
Paediatric population: A population PK study has been conducted in 74 hypertensive children aged from 1 to 17 years (with 34 patients aged 6 to 12 years and 28 patients aged 13 to 17 years) receiving amlodipine between 1.25 and 20 mg given either once or twice daily. In children 6 to 12 years and in adolescents 13-17 years of age the typical oral clearance (CL/F) was 22.5 and 27.4 L/hr respectively in males and 16.4 and 21.3 L/hr respectively in females. Large variability in exposure between individuals was observed. Data reported in children below 6 years is limited.

Preclinical safety data
Reproductive toxicology: Reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labour and decreased pup survival at dosages approximately 50 times greater than the maximum recommended dosage for humans based on mg/kg.
Impairment of fertility: There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg on a mg/m2 basis).
In another rat study in which male rats were treated with amlodipine besilate for 30 days at a dose comparable with the human dose based on mg/kg, decreased plasma follicle stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells.
Carcinogenesis, mutagenesis: Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m2 basis) was close to the maximum tolerated dose for mice but not for rats. Mutagenicity studies revealed no drug related effects at either the gene or chromosome levels.
*Based on patient weight of 50 kg

6. HOW TO STORE AMEDIN
KEEP THIS MEDICINE OUT OF THE SIGHT AND REACH OF CHILDREN
Do not use this medicine after the expiry date which is stated on the pack after 'EXP'. The expiry date refers to the last day of that month.
Store below 30°C.
Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

7. FURTHER INFORMATION
What Amedin 5 mg contains
- The active substance is amlodipine.
- Each uncoated tablets contains 6.90mg amlodipine besilate equivalent to amlodipine 5mg.
- The excipients are maize starch (dry mix), lactose monohydrate, anhydrous calcium hydrogen phosphate, povidone polyvinyl pyrrolidone (K-30), purified talc, magnesium stearate, sodium starch glycolate, colloidal anhydrous silica

The excipient with known effect is: lactose.

What Amedin 5mg looks like and contents of the pack
White colored round uncoated tablets with bevel edges and marked with AM/5 on one side and plain on the other side.
Pack size: 2 × 14's
Primary packing: 14 Tablets are packed in blisters using aluminium foil and plain cold forming foil.
Secondary packing: Two such blisters are placed in a carton along with a leaflet.

What Amedin 10mg contains
- The active substance is amlodipine.
- Each uncoated tablets contains 13.8 mg amlodipine besilate equivalent to amlodipine 10mg.
- The excipients are maize starch(dry mix), maize starch (lubrication), lactose, anhydrous calcium hydrogen phosphate, povidone (polyvinyl pyrollidone) K-30, purified Talc, magnesium stearate, colloidal anhydrous silica (AEROSIL 200/ COLLO SILLIC DIOX), sodium starch glycolate.

The excipient with known effect is: lactose.

What Amedin 10mg looks like and contents of the pack
White colored round uncoated tablets marked with AM/10 on one side and plain on the other side.
Pack size: 2 × 14's
Primary packing: 14 Tablets are packed in one Alu-PVC clear film blister.
Secondary packing: Two such blisters are packed in a carton along with leaflet.
Not all pack size may be marketed in your country.

Manufacturer: **MEDREICH LIMITED**
4/3, Avalahalli, Anjanapura Post,
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Bangalore - 560 062, Karnataka, INDIA
For: SANOFI
SANOFI

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