PRODUCT MONOGRAPH

^{Pr}RAN™-Amlodipine

Amlodipine BesylateTablets, House Std.

2.5mg amlodipine (as amlodipine besylate)

Antihypertensive-Antianginal Agent

Ranbaxy Pharmaceuticals Canada Inc.
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Control# 181699

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
oral	Tablets: 2.5 mg	colloidal silicon dioxide, dibasic calcium phosphate anhydrous, magnesium stearate, microcrystalline cellulose and sodium starch glycolate.

INDICATIONS AND CLINICAL USE

Hypertension
RAN-Amlodipine (amlodipine besylate) is indicated in the treatment of mild to moderate essential hypertension.

Combination of amlodipine besylate with a diuretic, a beta-blocking agent, or an angiotensin converting enzyme inhibitor has been found to be compatible and showed additive antihypertensive effect.

Chronic Stable Angina
RAN-Amlodipine is indicated for the management of chronic stable angina (effort-associated angina) in patients who remain symptomatic despite adequate doses of beta-blockers and/or organic nitrates or who cannot tolerate those agents.

RAN-Amlodipine may be tried in combination with beta-blockers in chronic stable angina in patients with normal ventricular function. When such concomitant therapy is introduced, care must be taken to monitor blood pressure closely since hypotension can occur from the combined effects of the drugs.

CONTRAINDICATIONS

RAN-Amlodipine (amlodipine besylate) is contraindicated in patients with hypersensitivity to the drug or other dihydropyridines* and in patients with severe hypotension (less than 90 mmHg systolic).
*Amlodipine besylate is a dihydropyridine calcium channel blocker.

WARNINGS AND PRECAUTIONS

General

Beta-blocker withdrawal: RAN-Amlodipine gives no protection against the dangers of abrupt beta-blocker withdrawal and such withdrawal should be done by the gradual reduction of the dose of beta-blocker.

Cardiovascular

Increased Angina and/or Myocardial Infarction: Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration and/or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated

Outflow Obstruction (Aortic Stenosis):

RAN-Amlodipine should be used with caution in a presence of fixed left ventricular outflow obstruction (aortic stenosis).

Use in Patients With Congestive Heart Failure: Although generally calcium channel blockers should only be used with caution in patients with heart failure, it has been observed that amlodipinebesylate had no overall deleterious effect on survival and cardiovascular morbidity in both short-term and long-term clinical trials in these patients. While a significant proportion of the patients in these studies had a history of ischemic heart disease, angina or hypertension, the studies were not designed to evaluate the treatment of angina or hypertension in patients with concomitant heart failure.

Hypotension:

RAN-Amlodipine may occasionally precipitate symptomatic hypotension. Careful monitoring of blood pressure is recommended, especially in patients with a history of cerebrovascular insufficiency, and those taking medications known to lower blood pressure.

Peripheral Edema: Mild to moderate peripheral edema was the most common adverse event in the clinical trials (see **ADVERSE REACTIONS**). The incidence of peripheral edema was dose-dependent and ranged in frequency from 3.0 to 10.8% in 5 to 10 mg dose range. Care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Hepatic/Biliary/Pancreatic

Use in Patients with Impaired Hepatic Function: There are no adequate studies in patients with liver dysfunction and dosage recommendations have not been established. In a small number of patients with mild to moderate hepatic impairment given single dose of 5 mg, amlodipine half-life has been prolonged (see **ACTION AND CLINICAL**

PHARMACOLOGY, Pharmacokinetics). RAN-Amlodipine should, therefore, be administered with caution in these patients and careful monitoring should be performed. A lower starting dose may be required (see **DOSAGE AND ADMINISTRATION**).

Patients with severe hepatic impairment or hepatic failure:
Because amlodipinebesylateis extensively metabolized by the liver and the plasma elimination half-life (t 1/2) is 56 hours in patients with impaired hepatic function, it should be administered cautiously and at reduced dosages in patients with severely impaired hepatic function (see **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment**). Slow dose titration and careful monitoring are required in patients with severe hepatic impairment.

Special Populations

Pregnant Women: Although amlodipine was not teratogenic in the rat and rabbit some dihydropyridine compounds have been found to be teratogenic in animals. In rats, amlodipine has been shown to prolong both the gestation period and the duration of labor. There was no effect on the fertility of rats treated with amlodipine (see TOXICOLOGY, Reproduction And Teratology).There is no clinical experience with amlodipine besylate in pregnant women.RAN-Amlodipine should be used during pregnancy only if the potential benefit outweighs the potential risk to the mother and fetus.

Nursing Women: It is not known whether amlodipine is excreted in human milk. Since amlodipine safety in newborns has not been established, RAN-Amlodipine should not be given to nursing mothers.

Pediatrics (< 6 years of age): The use of RAN-Amlodipine is not recommended in patients less than 6 years of age since safety and efficacy have not been established in that population. Pediatric safety and efficacy studies beyond 8 weeks of duration have not been conducted.

The effect of amlodipinebesylate on blood pressure in patients less than 6 years of age is not known. The pediatric administration should be based on a careful risk/benefit assessment of the limited available information. The risk/benefit assessment should be conducted by a qualified physician.

Geriatrics: In elderly patients (≥65 years) clearance of amlodipine is decreased with a resulting increase in AUC (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**). In clinical trials the incidence of adverse reactions in elderly patients was approximately 6% higher than that of younger population (<65 years). Adverse reactions include edema, muscle cramps and dizziness. RAN-Amlodipine should be used cautiously in elderly patients. Dosage adjustment is advisable (see **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Amlodipine besylatehas been administered to 1,714 patients (805 hypertensive and 909 angina patients) in controlled clinical trials (vs placebo alone and with active comparative agents). Most adverse reactions reported during therapy were of mild to moderate severity.

HYPERTENSION
In the 805 hypertensive patients treated with amlodipinebesylate in controlled clinical trials, adverse effects wereereported in 29.9% of patients and required discontinuation of therapy due to side effects in 1.9% of patients.The most common adverse reactions in controlled clinical trials were: oedema (8.9%), and headache (8.3%).

The following adverse reactions were reported with an incidence of ≥0.5% in the controlled clinical trials program (n=805):

Cardiovascular: oedema (8.9%), palpitations (2.0%), tachycardia (0.7%), postural dizziness (0.5%).
Skin and Appendages: pruritus (0.7%).
Musculoskeletal: muscle cramps (0.5%).
Central and Peripheral Nervous System: headaches (8.3%), dizziness (3.0%), paraesthesia (0.5%).
Autonomic Nervous System: flushing (3.1%), hyperhidrosis (0.9%), dry mouth (0.7%).
Psychiatric: somnolence (1.4%).
Gastrointestinal: nausea (2.4%), abdominal pain (1.1%), dyspepsia (0.6%), constipation (0.5%).
General: fatigue (4.1%), pain (0.5%).

ANGINA
In the controlled clinical trials in 909 angina patients treated with Amlodipine besylate, adverse effects were reported in 30.5% of patients and required discontinuation of therapy due to side effects in 0.6% of patients. The most common adverse reactions reported in controlled clinical trials were: oedema (9.9%) and headache (7.8%).

The following adverse reactions occurred at an incidence of ≥0.5% in the controlled clinical trials program(n=909);

Cardiovascular: oedema (9.9%), palpitations (2.0%), postural dizziness (0.6%).
Skin and Appendages: rash (1.0%), pruritus (0.8%).
Musculoskeletal: muscle cramps (1.0%).
Central and Peripheral Nervous System: headaches (7.8%), dizziness (4.5%),

paraesthesia(1.0%),hypoaesthesia (0.9%).
Autonomic Nervous System: flushing (1.9%).
Psychiatric: somnolence (1.2%), insomnia (0.9%), nervousness (0.7%).
Gastrointestinal: nausea (4.2%), abdominal pain (2.2%), dyspepsia (1.4%), diarrhea (1.1%), flatulence (1.0%),constipation (0.9%).
Respiratory System: dyspnoea (1.1%).
Special Senses: visual impairment (1.3%), tinnitus (0.6%).
General: fatigue (4.8%), pain (1.0%), asthenia (1.0%).

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Amlodipine besylate has been evaluated for safety in about 11,000 patients with hypertension and angina. Thefollowing events occurred in <1% but >0.1% of patients in comparative clinical trials (double-blind comparativevs placebo or active agents; n = 2,615) or under conditions of open trials or marketing experience where acausal relationship is uncertain.

Cardiovascular: arrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, myocardial infarction,hypotension,peripheral ischemia, syncope, tachycardia, postural dizziness, postural hypotension, vasculitis, chest pain.
Central and Peripheral Nervous System: hypoaesthesia/paraesthesia, neuropathyperipheral, tremor, vertigo.
Gastrointestinal: anorexia, constipation, dysphagia, vomiting, gingival hyperplasia, change in bowel habits, dyspepsia.
General: allergic reaction, asthenia[+], back pain, pain, hot flushes, malaise, rigors, and weight increased/ weight decreased.
Musculoskeletal System: arthralgia, arthrosis, myalgia, muscle cramps.
Psychiatric: sexual dysfunction (male[+] and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization, mood altered.
Respiratory System:dyspnoea, epistaxis.
Skin and Appendages: pruritus, rash erythematous, rash maculopapular, erythema multiforme.
Special Senses: conjunctivitis, diplopia, eye pain, visual impairment,tinnitus.
Urinary System: pollakiuria, micturition disorder, nocturia.
Autonomic Nervous System: dry mouth, hyperhidrosis.
Metabolic and Nutritional: hyperglycaemia, thirst.
Hemopoietic: leukopenia, purpura, thrombocytopenia.
Reproductive system and breast disorders:gynecomastia, erectile dysfunction

[+] These events occurred in less than 1% in placebo controlled trials, but the incidence of these side effects wasbetween 1% and 2% in all multiple dose studies.

The following events occurred in ≤0.1% of patients: cardiac failure, skin discoloration*,urticaria*, skin dryness,Stevens-Johnson syndrome, alopecia*, twitching, ataxia, hypertonia*, migraine, apathy, amnesia, gastritis*,pancreatitis*, increased appetite, coughing*, rhinitis*,parosmia, taste perversion*, and xerophthalmia.
*these events were observed in marketing experience as well.

Isolated cases of angioedema have been reported. Angioedema may be accompanied by breathing difficulty.

Post-Market Adverse Drug Reactions

In postmarketing experience, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis or hepatitis) in some cases severe enough to require hospitalization have been reported in association with use of amlodipine.

Postmarketing reporting has also revealed cases of extrapyramidal disorders induced by amlodipine.

DRUG INTERACTIONS

Overview

As with all drugs, care should be exercised when treating patients with multiple medications. Dihydropyridine calcium channel blockers undergo biotransformation by the cytochrome P450 system, mainly via CYP 3A4 isoenzyme. Coadministration of amlodipine with other drugs which follow the same route of biotransformation may result in altered bioavailability of amlodipine or these drugs. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio, and especially in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered amlodipine to maintain optimum therapeutic blood levels.

Drug-Drug Interactions

Table 1 – Established or Potential Drug-Drug Interactions

Proper name	Ref	Effect	Clinical comment
Drugs known to be inhibitors of the cytochrome P450 system (diltiazem, azole antifungals, erythromycin, quinidine, terfenadine and warfarin)	CT T	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. Erythromycin co-administration in healthy volunteers (18 to 43 years of age) increased the systemic	These pharmacokinetic changes may be more pronounced in the elderly. Close monitoring and dose adjustment may be required.

Proper name	Ref	Effect	Clinical comment
		exposure of amlodipine by 22%.	
Strong inhibitors of CYP3A4(e.g., ketoconazole, itraconazole, ritonavir)	T	May significantly increase the plasma concentrations of amlodipine to a greater extent than diltiazem.	Amlodipine should be used with caution together with CYP3A4 inhibitors and monitoring of therapy is required. Appropriate dosage adjustment of amlodipine may be necessary when used with CYP3A4 inhibitors. Patients should be advised to seek medical attention if they experience edema or swelling of the lower extremities; sudden, unexplained weight gain; difficulty breathing; chest pain or tightness; or hypotension as indicated by dizziness, fainting, or orthostasis.
Drugs known to be inducers of the cytochrome P450 system include: phenobarbital, phenytoin, rifampin	T	There is no data available regarding the effect of CYP3A4 inducers on amlodipine. The concomitant use of CYP3A4 inducers may give a lower plasma concentration of amlodipine which in turn can result in decreased blood pressure lowering effects.	Amlodipine should be used with caution together with CYP3A4 inducers and dose adjustment may be necessary to maintain efficacy. Hence, monitoring of therapy is required.
Drugs known to be biotransformed via	T	Amlodipine has a low (rate of first-pass)	

Proper name	Ref	Effect	Clinical comment
P450 (benzodiazepines, flecainide, imipramine, propafenone, theophylline)		hepatic clearance and consequent high bioavailability, and thus, may be expected to have a low potential for clinically relevant effects associated with elevation of amlodipine plasma levels when used concomitantly with drugs that compete for or inhibit the cytochrome P450 system.	
Cimetidine, warfarin, digoxin	CT	Pharmacokinetic interaction studies with amlodipine in healthy volunteers have indicated that cimetidine did not alter the pharmacokinetics of amlodipine and that amlodipine did not change warfarin-induced prothrombin response time nor did it change serum digoxin levels or digoxin renal clearance in normal volunteers.	
Antacids	CT	Concomitant administration of Maalox (magnesium hydroxide and aluminum hydroxide) had no effect on the disposition of a single 5mg dose of amlodipine in 24	

Proper name	Ref	Effect	Clinical comment
		subjects.	
Beta- blockers	T	Blood pressure lowering effect of beta-blockers may be increased by amlodipine.	When beta-adrenergic receptor blocking drugs are administered concomitantly with amlodipine, patients should be carefully monitored since blood pressure lowering effect of beta-blockers may be augmented by amlodipine's reduction in peripheral vascular resistance.
Sildenafil	CT	A single 100 mg dose of sildenafil (Viagra) in subjects with essential hypertension had no effect on AUC or Cmax of amlodipine. When sildenafil (100 mg) was co-administered with amlodipine, 5 or 10 mg in hypertensive patients, the mean additional reduction of supine blood pressure was 8 mm Hg systolic and 7 mm Hg diastolic.	
Atorvastatin	CT	In healthy volunteers, co-administration of multiple 10 mg doses of amlodipine with 80 mg of atorvastatin resulted in no clinical significant change in the AUC (average of 18% increase) or Cmax or Tmax of	Close monitoring is required.

Proper name	Ref	Effect	Clinical comment
		atorvastatin.	
Simvastatin	CT	Co-administration of multiple doses of 10 mg of 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.
Cyclosporin	CT	No drug interaction studies have been conducted with cyclosporin and amlodipine in healthy volunteers or other populations with the exception of renal transplant patients. A prospective study in hypertensive renal transplant patients (N=11) showed on an average of 40% increase in trough cyclosporin levels when concomitantly treated with amlodipine.	Consideration should be given for monitoring cyclosporine levels in renal transplant patients on amlodipine.
Tacrolimus	C	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 adjustments of tacrolimus when appropriate.

Legend: CT=Clinical Trial; T=Theoretical; C=Case study

Drug- Food Interactions

Interaction with Grapefruit Juice: Published data indicate that through inhibition of the cytochrome P450 system, grapefruit juice can increase plasma levels and augment pharmacodynamic effects of some dihydropyridine calcium channel blockers. Co-administration of 240mL of grapefruit juice with a single oral dose of amlodipine 10 mg 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 (See **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**).Hence, monitoring of therapy is required.

Drug-Herb Interactions

St-John's Wort is an inducer of CYP3A4. The concomitant use of CYP3A4 inducers may give a lower plasma concentration of amlodipine which in turn can result in decreased blood pressure lowering effects.Amlodipine should be used with caution together with CYP3A4 inducers and dose adjustment may be necessary to maintain efficacy. Hence, monitoring of therapy is required.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Dosage should be individualized depending on patient's tolerance and responsiveness.

Recommended Dose and Dosage Adjustment

For both hypertension and angina, the recommended initial dose of RAN-Amlodipine (amlodipine besylate) is 5 mg once daily. If necessary, dose can be increased after 1-2 weeks to a maximum dose of 10 mg once daily.

Use in the Elderly or in Patients with Impaired Renal Function: The recommended initial dose in patients over 65 years of age or patients with impaired renal function is 5 mg once daily. If required, increasing in the dose should be done gradually and with caution (see **WARNINGS AND PRECAUTIONS**).

Use in Patients with Impaired Hepatic Function: Dosage requirements have not been established in patients with impaired hepatic function. When RAN-Amlodipineis used in these patients, the dosage should be carefully and gradually adjusted depending on patients tolerance and response. A lower starting dose of 2.5 mg once daily should be considered (see **WARNINGS AND PRECAUTIONS**).

Use in Pediatric Patients (6 – 17 years of age): The effective antihypertensive oral dose in pediatric patients ages 6-17 years is 2.5 mg to 5 mg once daily. Doses in excess of 5 mg daily

have not been studied; dose should be determined based upon the medical need of the patients(See **ACTION AND CLINICAL PHARMACOLOGY)**.

OVERDOSAGE

Symptoms: Overdosage can cause excessive peripheral vasodilation with marked and probably prolonged hypotension and possibly a reflex tachycardia. In humans, experience with overdosage of amlodipine besylateis limited. When amlodipine was ingested at doses of 105-250 mg some patients remained normotensive with or without gastric lavage while another patient experienced hypotension (90/50 mmHg) which normalized following plasma expansion. A patient who took 70 mg of amlodipine with benzodiazepine developed shock which was refractory to treatment and died. In a 19 month old child who ingested 30 mg of amlodipine (about 2 mg/kg) there was no evidence of hypotension but tachycardia (180 bpm) was observed. Ipecac was administered 3.5 hrs after ingestion and on subsequent observation (overnight) no sequelae were noted.

Treatment:

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Clinically significant hypotension due to overdosage requires active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output. A vasoconstrictor (such as norepinephrine) may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. As amlodipine is highly protein bound, hemodialysis is not likely to be of benefit. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade. Clearance of amlodipine is prolonged in elderly patients and in patients with impaired liver function. Since amlodipine absorption is slow, gastric lavage may be worthwhile in some cases.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

RAN-Amlodipine (amlodipine besylate) is a calcium ion influx inhibitor (calcium entry blocker or calcium ion antagonist). Amlodipine is a member of the dihydropyridine class of calcium antagonists.

The therapeutic effect of this group of drugs is believed to be related to their specific cellular action of selectively inhibiting transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. The contractile processes of these tissues are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Serum calcium concentration is not affected by amlodipine. Within the physiologic pH range, amlodipine is an ionized

compound and its kinetic interaction with the calcium channel receptor is characterized by the gradual association and dissociation with the receptor binding site. Experimental data suggest that amlodipine binds to both dihydropyridine and nondihydropyridine binding sites.

A. Hypertension The mechanism by which amlodipine reduces arterial blood pressure involves direct peripheral arterial vasodilation and reduction in peripheral vascular resistance.

B. Angina The precise mechanism by which amlodipine relieves angina has not been fully delineated. Amlodipine is a dilator of peripheral arteries and arterioles which reduces the total peripheral resistance and, therefore, reduces the workload of the heart (afterload). The unloading of the heart is thought to decrease ischemia and relieve effort angina by reducing myocardial energy oxygen consumption and oxygen requirements.

Pharmacodynamics

Hemodynamics: Following administration of recommended doses to patients with hypertension, amlodipine produces vasodilation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by any significant change in heart rate or plasma catecholamine levels with chronic dosing. With chronic once daily oral administration (5 and 10 mg once daily), antihypertensive effectiveness is maintained throughout the 24 hours dose interval with minimal peak to trough differences in plasma concentration. Since the vasodilation induced by amlodipine is gradual in onset, acute hypotension has rarely been reported after oral administration of amlodipine. In normotensive patients with angina amlodipine has not been associated with any clinically significant reductions in blood pressure or changes in heart rate.

Negative inotropic effects have not been observed when amlodipine was administered at the recommended doses to man, but has been demonstrated in animal models. Hemodynamic measurements of cardiac function at rest and during exercise (or pacing) in angina patients with normal ventricular function have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume.

In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow without change in filtration fraction.

Electrophysiologic Effects: Amlodipine does not change sinoatrial nodal function or atrioventricular conduction in intact animals, or man. In patients with chronic stable angina, intravenous administration of 10 mg of amlodipine and a further 10 mg of amlodipine after a 30 min. interval produced peripheral vasodilation and afterload reduction, but did not significantly alter A-H and H-V conduction and sinus node recovery time after pacing. Similar results were obtained in patients receiving amlodipine and concomitant beta-blockers. In clinical studies in which amlodipine was administered in combination with beta-blockers to patients with either hypertension or angina, no adverse effects on electrocardiographic parameters were observed. In

clinical trials with angina patients, amlodipine as monotherapy did not alter electrocardiographic intervals.

Effects in Hypertension

Pediatric Patients

Two hundred sixty-eight hypertensive patients aged 6 to 17 years were randomized first to amlodipine besylate 2.5mg or 5 mg once daily for 4 weeks and then randomized again to the same dose or to placebo for another 4 weeks. Patients receiving 5 mg at the end of 8 weeks had lower blood pressure than those secondarily randomized to placebo. The magnitude of the treatment effect is difficult to interpret, but it is probably less than 5 mmHg systolic on the 5 mg dose. Adverse events were similar to those seen in adults.

Pediatric safety and efficacy studies beyond 8 weeks of duration have not been conducted. In addition, the long-term effect of amlodipine on growth and development, myocardial growth and vascular smooth muscles has not been studied.

Pharmacokinetics

Absorption: After oral administration of therapeutic doses of amlodipine, absorption occurs gradually with peak plasma concentration reached between 6 and 12 hours. Absolute bioavailability has been estimated to be between 64 and 90%. The bioavailability of amlodipine is not altered by the presence of food.

Metabolism: Amlodipine is metabolized through the cytochrome P450 system, mainly via CYP 3A4 isoenzyme. Amlodipine is extensively (about 90%) converted to inactive metabolites (via hepatic metabolism) with 10% of the parent compound and 60% of the metabolites excreted in the urine. Ex vivo studies have shown that approximately 93% of the circulating drug is bound to plasma proteins in hypertensive patients.

Excretion: Elimination from the plasma is biphasic with a terminal elimination half-life of about 35-50 hours. Steady state plasma levels of amlodipine are reached after 7 to 8 days of consecutive daily dosing.

Special Populations and Conditions

Following oral administration of 10 mg amlodipine to 20 male volunteers, pharmacokinetics of amlodipine, geometric mean Cmax of amlodipine was 6.2 ng/mL when the drug was administered with grapefruit juice and 5.8 ng/mL when administered with water. Mean Tmax of amlodipine was 7.6 hours with grapefruit juice and 7.9 hours withwater. Geometric mean $AUC_{0-\infty}$ was 315 ng/hr/mL with grapefruit juice and 293 ng/hr/mL with water. Geometric mean bioavailability of amlodipine was 85% when administered with grapefruit juice and 81% when administered with water.

Pediatrics: Two studies were conducted to evaluate the use of amlodipine besylate in a pediatric population.

In one study (pharmacokinetic), sixty-two hypertensive patients aged greater than 6 years received doses of amlodipine besylate between 1.25 mg and 20 mg. Weight-adjusted clearance and volume of distribution were similar to values in adults (see **DOSAGE AND ADMINISTRATION**). The mean absorption rate constant (K_a) in children (0.85 hr^{-1}) is approximately 50% higher than that in healthy adults (0.55 hr-1, range of 0.28–1.09 hr^{-1}).

Gender effect: In a second trial (clinical), a pattern of greater reductions in both systolic and diastolic blood pressure in females than in males was observed. Mean change in systolic blood pressure from baseline to end of study: amlodipine 2.5 mg: males, -6.9 mmHg (n=51); females, -8.9 mmHg (n=32); amlodipine 5.0 mg: males, -6.6 mmHg (n=63); females, -14.0 mmHg (n=23); placebo males, -2.5 mmHg (n=54), females, -3.8 mmHg (n=33).

Renal Insufficiency: The pharmacokinetics of amlodipineare not significantly influenced by renal impairment. Plasma concentrations in the patients with moderate to severe renal failure were higher than in the normal subjects. Accumulation and mean elimination half-life in all patients were within the range of those observed in other pharmacokinetic studies with amlodipine in normal subjects.

Geriatrics: In elderly hypertensive patients (mean age 69 years) there was a decrease in clearance of amlodipine from plasma as compared to young volunteers (mean age 36 years) with a resulting increase in the area under the curve (AUC) of about 60%.

Hepatic Insufficiency: Following single oral administration of 5 mg of amlodipine, patients with chronic mild-moderate hepatic insufficiency showed about 40% increase in AUC of amlodipine as compared to normal volunteers. This was presumably due to a reduction in clearance of amlodipine as the terminal elimination half-life was prolonged from 34 hrs in young normal subjects to 56 hrs in the elderly patients with hepatic insufficiency.

Patients with severe hepatic impairment or hepatic failure:
Because amlodipine is extensively metabolized by the liver and the plasma elimination half-life ($t_{1/2}$) is 56 hours in patients with impaired hepatic function, it should be administered cautiously and at reduced dosages in patients with severely impaired hepatic function (see **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment**). Slow dose titration and careful monitoring are required in patients with severe hepatic impairment.

STORAGE AND STABILITY

Store at 15-30°C. Protect from light.

DOSAGE FORMS, COMPOSITION AND PACKAGING

RAN-Amlodipine are available as white to off-white, tablets containing amlodipine besylate equivalent to 2.5mgamlodipine per tablet.

2.5mg: Available as white to off-white, round, flat faced beveled edge tablets “211” debossed on one side and plain on other side.

Supplied in white high density polyethylene bottles of 100, 250 and 500 tablets of each strength.

RAN-Amlodipine tablets contain amlodipine besylate equivalent to 2.5mgof amlodipine per tablet.

Also contains the following non-medicinal ingredients: microcrystalline cellulose, dibasic calcium phosphate anhydrous, sodium starch glycolate, colloidal silicon dioxide and magnesium stearate.

PART II: SCIENTIFIC INFORMATION

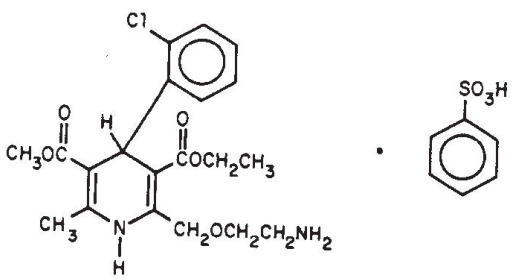
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: amlodipine besylate

Chemical Name: 3-Ethyl-5-methyl-2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-1,4-dihydro-6 methyl-3,5-pyridinedicarboxylate benzenesulphonate.

Structural Formula:



Molecular Formula: $C_{20}H_{25}ClN_2O_5.C_6H_6O_3S$

Molecular Weight: 567.1 g/mol

Description: Amlodipine Besylate is a white crystalline substance, slightly soluble in water and sparingly soluble in ethanol.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Open labeled, randomized two-treatment, two-period, two-sequence single dose, crossover bioequivalence study of RAN-Amlodipine 10mg tablets (Ranbaxy Pharmaceuticals Canada Inc.), compared with Norvasc containing Amlodipine Besylate 10mg tablets (Pfizer Canada Inc., Canada) in 26 healthy adult Asian male subjects under fasted conditions

Amlodipine (one x 10 mg) From measured data Geometric Mean Arithmetic Mean (CV %)					
Parameter	RAN-Amlodipine*	Norvasc†	% Ratio of Geometric Means	90% Confidence Interval	
				Lower	Upper
AUC_{0-72} (pg.hr/mL)	271925.158 282796.845 (24.98)	268671.050 276369.262 (23.27)	101.21	94.16	108.79
AUC_I (pg.hr/mL)	426332.899 442973.413 (25.13)	427386.735 443897.382 (27.61)	99.75	92.76	107.27
C_{max} (pg/mL)	7710.569 8081.770 (30.12%)	7805.832 8109.152 (27.64%)	98.78	91.41	106.74
T_{max}€ (hr)	6.770 (35.07)	6.885 (31.64)			
$T_{½}$€ (hr)	43.549 (19.32)	47.488 (15.46)			

* RAN-Amlodipine, by Ranbaxy Pharmaceuticals Canada Inc.
† Norvasc, Manufactured by Pfizer Canada Inc, Canada (purchased in Canada)
€ Expressed as the arithmetic mean (CV%) only

DETAILEDPHARMACOLOGY

ANIMAL

a. Mechanism of Action Studies - In Vitro

Amlodipine inhibited both calcium-induced and potassium-depolarisation-induced contractions of rat aorta. The inhibitory effect was gradual. The potency of amlodipine was more than 10-fold greater against Ca^{2+}-responses than against K^{+}-responses. Studies in both rat aorta and dog coronary artery indicated that amlodipine was a competitive antagonist. Radioligand binding experiments designed to characterize the interactions of amlodipine with calcium channel binding sites in bovine brain and in cardiac membranes from dog and rat showed that amlodipine interacts competitively and at high affinity with the dihydropyridine (DHP) recognition site.

Amlodipine has been demonstrated to block constriction of coronary arteries and arterioles in response to calcium, potassium, epinephrine, serotonin, and thromboxane A_2 analog in experimental animal models and in human coronary vessels in vitro.

Electrophysiological experiments conducted using isolated papillary muscles from guinea pig hearts confirmed that amlodipine was a highly selective calcium channel blocker which inhibited cardiac slow action potentials in a non-use-dependent manner and with no effect on the fast Na^{+}-channel.

In Langendorff-perfused guinea pig hearts, amlodipine showed negative inotropic activity, the concentration producing a 50% inhibition of cardiac contraction being approximately 10 times greater (20.2 nM) than for a 50% inhibition of vascular muscle contraction (1.9 nM). The drug displayed modest negative chronotropic effect (approximately 20%) at a concentration of 50 nM, approximately twice that required for 50% inhibition of cardiac contraction in the same preparation. Using Langendorff-perfused rat hearts the concentration producing a 50% inhibition of cardiac contraction was 300 times greater than for inhibition of coronary artery contraction.

b. Cardiovascular Activity - In Vivo

In anesthetized dogs, amlodipine (i.v. 25-1600 μg/kg) was a potent coronary and peripheral vasodilator; ED_{50} values were 103 and 212 μg/kg for reductions of coronary and systemic vascular resistances respectively. The reductions in vascular resistance were associated with corresponding increases in cardiac output, coronary flow, heart rate and myocardial contractility. Amlodipine possessed slow onset of action, minimal effect on blood pressure, and a long duration of action. Amlodipine caused slight, transient negative inotropic responses only at the highest dose, in excess of that required to cause maximal vasodilatation. The drug did not adversely affect atrial ventricular conduction, as assessed by PR interval.

Oral administration of amlodipine (0.5 to 2.0 mg/kg) to conscious dogs produced dose-related reductions in systemic vascular resistance (max. of 78%) and reflexly-induced increases in heart rate cardiac output and myocardial contractility; maximum effects were achieved much later (3 to 5 h) than after parenteral administration (5 to 30 min) which may explain the dose-related modest blood pressure reductions (max. change of 25%) observed by the oral route.

c. Antihypertensive Efficacy - In Vivo

Amlodipine produced dose-related reductions in blood pressure of spontaneously hypertensive rats (SHR) after oral administration. The antihypertensive effect was maintained for at least 6 h after each one of the 3 doses used (1, 3, and 10 mg/kg). In young SHR the development of hypertension was attenuated by 60% over a 12 week period when amlodipine was added to the diet to provide the dose of 8 mg/kg/day. In mature SHR receiving amlodipine for 8 weeks, a marked antihypertensive effect was evident by day 2 and attained a maximum by day 5. This effect was maintained for the remaining treatment period with no change in heart rate. In addition, treated animals showed a small, but statistically significant, reduction in ventricular weight and marked elevation in plasma renin activity.

In conscious renal-hypertensive dogs, oral administration of single doses of amlodipine (0.25, 0.5 and 1.0 mg/kg) produced dose-related reductions in blood pressures with maximum effects occurring at 5 h after dose. These responses were accompanied by dose-related increases in heart rate.

The slow onset and long-lasting antihypertensive effects of amlodipine were confirmed in conscious renal-hypertensive dogs in which blood pressure was recorded continuously for 24h.

In conscious renal-hypertensive dogs, orally-administered amlodipine (0.025, 0.05 and 0.25 mg/kg/day) for 10-14 days produced progressive reductions in the daily, resting, pre-dose blood pressure which stabilized after 4 or 5 days. The minimum blood pressures achieved each day were approximately equivalent and tolerance did not develop. Heart rate was inconsistently affected.

d. General Pharmacology

In both normotensive (fluid-loaded) and spontaneously hypertensive rats (SHR) amlodipine produced diuresis and natriuresis. A diuretic effect was also observed in saline loaded conscious or anesthetized dogs treated with low intravenous doses (less than 0.4 mg/kg) of amlodipine; increases in potassium excretion were not significant. Also in the conscious rat amlodipine produced dose-related reduction of basal gastric acid secretion and a small but significant reduction in gastro-intestinal motility. Experiments in anesthetized dogs indicated that phenylephrine was an effective antidote to the hypotensive effect of a supra-maximal dose of amlodipine.

TOXICOLOGY

Acute Toxicity:
Amlodipine (as maleate unless otherwise indicated)

Species	Sex	Route	LD_{50}	Range of Lethal Doses (mg/kg)	
			base/mg/kg	No Deaths	All Dead
Mice	M	p.o.	N.D.	10	40
	F	p.o.	N.D.	10	40
	M	i.v.	N.D.	2.5	10
	F	i.v.	N.D.	2.5	10
Rats	M	p.o.	150	2/10 at 100	400
	F	p.o.	140	2/10 at 100	250
	M	i.v.	N.D.	1	10
	F	i.v.	N.D.	1	10
Rats*	M	p.o.	393**		
	F	p.o.	686**		

* Sprague Dawley Rats from Shizouka Lab Animal Centre Hamamatsu, Japan
** Besylate Salt
\+ Dogs from Interfauna, France
++ Dogs from Japan
N.D. Not Determined: The result did not permit calculations of LD_{50} values. Thus, range of lethal doses is given.

The main clinical signs in the oral studies were somnolence, decreased spontaneous movement and for rats salivation, dyspnea, ptosis, lacrimation, blanching, cyanosis, rough coat, abdominal distension, and eventually coma. After i.v. injection, the animals died rapidly showing only somnolence, tachypnea or ptosis.

SPECIES	ROUTE	DOSE base mg/kg/day	ANIMAL PER DOSE LEVEL	DURATION	FINDINGS
Maximum Tolerated Dose (Single):					
Dog	Oral (gavage)	4 8 16	2 M	Single Dose	At all dose levels: Vasodilation and increases in plasma aldosterone levels. At 4 mg/kg: Compensatory tachycardia. At 8 mg/kg: In 1 of 2 dogs vomiting, sedation, respiratory distress and diarrhea 48 hr post-dose; normal at day 5. Compensatory tachycardia. At 16 mg/kg: Moribund with hyperthermia within 24 hours; low blood pressure returned to normal over 2-6 days; transient raise in heart rate. Histological examination showed congestion, edema and hemorrhage of the right atrial wall in the 2 dogs at 16 mg/kg. The hemorrhage in the right atrial wall corresponds to the right atrial lesions seen in long-term studies with amlodipine and other vasodilators (see long-term toxicity). One of 2 dogs at each dose showed fibrosis of the left ventricle in the subendocardial region and the posterior papillary muscle. The maximum tolerated dose was not determined.
Dog (Japanese Study)	Oral	3.5 7	1 M 1 F	Single Dose	Mortality: 1 male dog at 7 mg/kg. Decreased spontaneous movement and flushing of palpebral conjunctiva and buccal cavity. At 7 mg/kg: 1 female vomiting: 1 male hypothermia, lying prone. Hematology/Clinical Chemistry: Increase in WBC and BUN at 10 and 5 mg/kg (males). The maximum tolerated dose was not determined.
Subacute And Chronic Toxicity:					
Mouse	Oral (diet)	0 2.5 5 10	10 M 10 F	2 Months	At 10 mg/kg/day: Mice died during week 2 of the study. At 5 mg/kg/day (males and females) and 2.5 mg/kg/day (males): Increase in water consumption. At 5 mg/kg/day -Pathology: Drug-related increases in heart and liver weights.

SPECIES	ROUTE	DOSE base mg/kg/day	ANIMAL PER DOSE LEVEL	DURATION	FINDINGS
Rat (Japanese Study)	Oral (gavage)	0 4 16 32 64	12 M 12 F	1 Month	At 64 mg/kg/day: All rats died within 9 days. At 32 mg/kg/day: 12/24 rats died; decreased food consumption, growth inhibition, ptosis, decreased spontaneous movement. At 16 and 32 mg/kg/day: The pattern of results on heart weights, increased urinary volume, effect on electrolyte balance and the adrenals was similar to that of the 6 month study below; increase in BUN at 16 mg/kg (males) and at 32 mg/kg (males and females).
Rat (Japanese Study)	Oral (gavage)	0 2 7 21	16 M 16 F	3 Months followed by 1 Month drug withdrawal	21 mg/kg/day: Salivation, growth inhibition, increased BUN, increased urinary volume, effect on electrolyte balance and adrenals was similar to that of the 6 month study below. Also post-mortem dilation of small intestine without morphological lesions. At 7 mg/kg/day: Alterations in urinary electrolytes excretion. No drug related effects at the end of 1 month drug withdrawal phase.
Rat	Oral (gavage)	0 2.5 5 10	20 M 20 F	6 Months	At all dose levels: Renal effects: increased urinary volume and/or Na/K/Cl excretion, decreased plasma Na/K and/or Ca/Cl and increased urea; Post-mortem: Increase in heart weights. At 10 mg/kg/day: Renal effects: increased kidney weight. Histopathology: Thickening of zonaglomerulosa at 5 and 10 mg/kg/day.
Rat (Japanese Study)	Oral (gavage)	1.4 7 18	30 M 30 F	12 Months (interim sacrifice 5/sex/group after 6 months)	Mortality: 3 rats (2 males and 1 female) at 18 mg/kg/day. At 18 mg/kg/day: Salivation, growth inhibition; Renal effects: increase in urinary volume with increased electrolytes excretion and decreased serum electrolytes; increase in BUN. At 7 mg/kg/day: Growth inhibition (males); Renal effects: increases of urinary volume and electrolyte excretion. Post-mortem: Increases of adrenal weights (at 18/mg/kg), increases of relative heart weight (18 and 7 mg/kg), dilated small intestines without morphological change (18 mg/kg). Histopathology - Main Finding: Enlargement of the zonaglomerulosa of the adrenals (18 and 7 mg/kg).

SPECIES	ROUTE	DOSE base mg/kg/day	ANIMAL PER DOSE LEVEL	DURATION	FINDINGS
Dog	Oral (gavage)	0.5 to 4	2 M 2 F	10 Days Supple-mentary Dose Escalation Study (0.5 mg/kg/day)	At 4 mg/kg: Death of all (4/4) dogs preceded in 3 dogs by low systolic blood pressure, bradycardia, disturbances of heart rhythm and conduction. Clinical signs included pale skin, hypothermia and prostration. Histopathology: Showed foci of myocyte necrosis and sarcoplasmic vacuolation in the left ventricle, papillary muscle and left and right atria. Congestion and/or edema in several organs (i.e. gastrointestinal tract/gall bladder wall and surrounding tissues as well as the connective tissue surrounding both kidneys).
Dog	Oral	0 0.25 0.5 1	3 M 3 F	6 Months	At all dose levels: Increase in urinary volume and urinary excretion of electrolytes (not dose-related). Reduction in blood pressure and increases in heart rate. At 1 mg/kg/day - Pathology: Increase in relative heart weights in 4/6 dogs, inflammatory lesion of the right atrial wall was seen which was considered to be consequence of excessive hemodynamic changes.
Dog	Oral	0 0.125 0.25 0.5	4 M 4 F	12 Months	At 0.5 mg/kg/day: Reduction in blood pressure and increases in heart rate; increase in urinary volume and urinary excretion of electrolytes (females). At 0.5 mg/kg/day - Pathology: Showed inflammatory lesions of the right atrial wall in 1/8 dogs, similar to that of the 6 month study above, and diffuse gingival hyperplasia.

Mutagenicity:

Study	Test Organism	Dose	Route	Major Findings
Ames Test (modified) Quantitative Plate Assay (QAP) and Metabollic Activation (MA) with Hepatic Microsomes	salmonellatyphimurium: Strains TA 1535. TA 1537, TA 98 and TA 100.	10-0.02 mg/plate (QAP) 0.2-0.0005 mg/plate (MA)	In-vitro	No evidence of mutation frequency.
Invivo Cytogenetic Tests	mouse bone marrow	20 mg/kg single dose 10mg/kg/day for 5 days	In-vivo p.o s.c	No indication of chromosome breakage or mutagenicity observed

Study	Test Organism	Dose	Route	Major Findings
In-vitro Cytogenetic Tests With or without metabolic activation [rat liver microsomal enzymes (S-9)]	Human lymphocytes	Without metabolic activation: 0.01 to 1000 µg/MI of culture medium with metabolic activation 1.0 to 25µg/MI of culture medium	In-vitro	Non-activation: No evidence of induced chromosome breakage observed at levels of 1.0µg/ml and below. At levels higher that 1.0µg/ml, compound produced mitotic inhibition. Activation: No drug induced clastogenic activity observed at levels up to 10 µg/ml. higher levels produced mitotic inhibition.
Quantitative Plate Assay (QAP) of Mouse Urine	Salmonella typhimuriumStrains: TA 1535, TA 1537, TA 98 and TA 100.	0, 1, 10 and 20 mg/kg	In-vivo p.o	No incidence of an excreted mutagen
L 5178Y/TK ± Gene Mutation Assay with and without liver S-9 fraction	Mouse lymphoma cells	1.2 – 38 µg/ml	In-vitro	No evidence of gene mutational activity.

Carcinogenicity:

There was no evidence of a carcinogenic effect when amlodipine was administered in the diet for up to 24 months to rats up to 2.5 mg/kg/day. Amlodipine was also administered for up to 24 months of dietary administration to mice at doses up to 2.5 mg/kg/day and no evidence of carcinogenicity was observed.

Reproduction And Teratology:

Species	Route	Dose base/mg/kg/day	Animal per Dose Level	Duration	Findings
Fertility					
Rat (SD) (Japanese Study)	Oral (gavage)	0 1.4 7 18	24 M + 24 F	Males 71 days prior to and during mating. Females 14 days prior to and during mating and up to 7 days of gestation.	At 18 mg/kg: Impairment of body weight gain (females). There were no effects of the drug on copulation or pregnancy rates, nor any evidence of embryotoxicity or teratogenicity.
Teratology					
Rat (Charles River CD/SD)	Oral (gavage)	0 2 5 10	20 F	Days 6-15 post insemination. Hysterectomies on day 20 of gestation.	No effects were observed.
Rat (SD) Japanese Study	Oral (gavage)	0 3 7 18	34 F	Days 7-17 post-insemination. 2/3 of dams sacrificed on day 21 of gestation. F1 generation followed.	No effects were observed except in the dams. At 18 mg/kg: Reduction in food intake and body weight gain.
Rabbit (Japanese White) Japanese Study	Oral	0 3 7 18	18 or 19 F	Day 6 to day 18 of gestation.	At 18 and 7 mg/kg: Decrease in maternal body weight (18 mg/kg) decrease in food consumption (18 and 7 mg/kg). No evidence of drug induced fetotoxicity or teratogenicity.
Peri- and Post-Natal					
Rat (SD) Japanese Study	Oral (gavage)	0 1.4 2.8 7.0	25 F	Day 17 of gestation to day 21 post-partum.	As in the combined Fertility/Perinatal Study above; at the high dose level (7.0 mg/kg/day) adverse effects were observed on parturition and number of viable pups at birth and day 4 post-partum.

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PART III: CONSUMER INFORMATION

PrRAN-AMLODIPINE
(Amlodipine Besylate Tablets, House std.)

This leaflet is part III of a three-part "Product Monograph" published when RAN-AMLODIPINE was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about RAN-AMLODIPINE. Contact your doctor, nurse or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
RAN-AMLODIPINEhas been prescribed to you for:
- The treatment of high blood pressure (hypertension), or
- The management of a type of chest pain called angina.

RAN-AMLODIPINEcan be used by itself or with other medicines to treat these conditions.

What it does:
RAN-AMLODIPINEis a type of medicine known as a calcium channel blocker (CCB).
RAN-AMLODIPINErelaxes your blood vessels, which lets your blood flow more easily and helps lower your blood pressure.
RAN-AMLODIPINEcontrols chest pain by improving the supply of blood and oxygen to the heart and by reducing its workload.

When it should not be used:
Do not use RAN-AMLODIPINEif you:
- Are allergic to amlodipine (the active ingredient in RAN-Amlodipine), or to the inactive ingredients listed under "**What the nonmedicinal ingredients are**" below.
- Have ever had an allergic reaction to a similar type of drug.
- Have very low blood pressure (less than 90 mmHg systolic).

What the medicinal ingredient is:
Amlodipine besylate

What the nonmedicinal ingredients are:
colloidal silicon dioxide, dibasic calcium phosphate anhydrous, magnesium stearate, microcrystalline cellulose and sodium starch glycolate.

What dosage forms it comes in:
Tablets 2.5 mg amlodipine

WARNINGS AND PRECAUTIONS

BEFORE you use RAN-AMLODIPINEtalk to your doctor, nurse or pharmacist if you:
- Ever had heart or blood vessel diseases.
- Have aortic stenosis (narrowing of a valve of your heart).
- Have liver or kidney problems.
- Are pregnant, or plan to become pregnant. RAN-AMLODIPINEshould not be used during pregnancy unless your doctor tells you otherwise.
- Are breast-feeding. Do not breast-feed while taking RAN-AMLODIPINE.
- Are older than 65 years.

RAN-AMLODIPINEmay occasionally cause low blood pressure (hypotension). Your blood pressure should be carefully monitored, especially if you have had a stroke or take other drugs to lower your blood pressure.

If you takeRAN-AMLODIPINEtogether with a drug known as beta-blockers (*e.g.* acebutolol, atenolol, metoprolol, nadolol), do not suddenly stop using the beta-blocker. If your doctor advises you to discontinue use of the beta-blocker, your dose should be decreased slowly, as recommended by your doctor, before stopping it completely.

RAN-AMLODIPINE is not recommended for use in children less than 6 years of age.

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. Tell your doctor, nurse or pharmacist about all medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines. Also mention if you drink alcoholic beverages.

Drug-Drug interaction:
Drugs that may interact with RAN-AMLODIPINEinclude:

- Cyclosporin
- Erythromycin, an antibiotic
- Diltiazem
- Azoleantifungals (*e.g.* ketoconazole, itraconazole)
- HIV protease inhibitors (*e.g.* ritonavir)
- Beta-blockers
- Sildenafil (VIAGRA)
- Statin drugs used to treat high cholesterol (e.g. Simvastatin, Atorvastatin)
- Tacrolimus (an anti-rejection drug)

Drug-Herb interaction:

- St-John Wort

Drug-Food interaction:
Do not eat grapefruit or drink grapefruit juice while on RAN-AMLODIPINE.

PROPER USE OF THIS MEDICATION

Take RAN-AMLODIPINE exactly as prescribed by your doctor, nurse or pharmacist. It may be easier to take your dose if you do it at the same time every day, such as with breakfast or dinner, or at bedtime. Do not stop taking your medication without having first informed your doctor.

Usual dose:
For both high blood pressure and chest pain, the recommended initial dose of RAN-Amlodipineis 5 mg once daily. If necessary, your doctor may increase your dose to a maximum dose of 10 mg once daily.

Use in Patients with liver disease:
The starting dose is 2.5 mg once daily and can be gradually increased by your doctor.

Use in Children (6-17 years old):
The recommended dose is 2.5 mg to 5 mg once daily.

Overdose:

If you think you have taken too much RAN-AMLODIPINE contactyour doctor, nurse pharmacist, hospital emergency department or regional Poison control Centre immediately, even if there are no symptoms.

One or more of the following signs may occur in an overdose: Low blood pressure and rapid heartbeat.

Missed Dose:
If you miss a dose, take it as soon as you remember. If it has been more than 12 hours since you missed your last dose, skip the missed dose and continue with the next dose at your regular time. Do not take double doses.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects include:

- Headaches
- Tiredness, extreme sleepiness
- Stomach pain, nausea
- Dizziness

If any of these affects you severely, tell your doctor, nurse or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptoms / effect		Talk with your doctor, nurse or pharmacist		Stop taking drug andseek immediate emergency medical help.
		Only if severe	In all cases	
Common	**Flushing:** Hot or warm feeling in your face	✓		
	Edema: Swelling of your legs or ankles	✓		
Uncommon	**Arrythmia :** Rapid, slow or irregular heartbeat		✓	
	Increased frequency, severity, duration of angina: Pressing or squeezing pain in your chest		✓	
	Heart Attack: Pain, fullness		✓	✓

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptoms / effect		Talk with your doctor, nurse or pharmacist		Stop taking drug andseek immediate emergency medical help.
		Only if severe	In all cases	
	and/or squeezing of the chest, jaw painand/or arm pain, shortness of breath			
	Liver Disorder: Yellowing of the skin or eye, dark urine, abdominal pain, nausea, vomiting, loss of appetite		✓	
	Allergic Reactions: Rash, hives, swelling of the face,lips, tongue or throat, difficulty breathing or swallowing			✓
	Low blood Pressure: Dizziness,fainiting, lightheadedness May occur when you go from lying or sitting to standing up	✓		
Unknown	**Extrapyramidal symptoms :** Muscle stiffness, body spasms, upward eye rolling, exaggeration of reflexes, drooling, difficulty moving how and when we want.			✓

This is not a complete list of side effects. For any unexpected effects while taking RAN-AMLODIPINE, contact your doctor, nurse or pharmacist.

HOW TO STORE IT

Keep RAN-AMLODIPINEout of the reach and sight of children. Store RAN-AMLODIPINETablets at room temperature (between 15-30^{0}C). Protect RAN-AMLODIPINEfrom light.

ReportingSide Effects

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

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3 ways to report:

- **online at www.healthcanada.gc.ca/medeffect;**
- **By calling 1-866-234-2345 (toll-free);**
- **By completing a Consumer Side Effect Reporting Form and sending it by:**
  - **Fax to 1-866-678-6789 (toll-free), or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are availableatMedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Contact your health professional if you need information about how to manage you side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about RAN-AMLODIPINE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by contacting Ranbaxy Pharmaceuticals Canada Inc. at 1-866-840-1340.

This leaflet was prepared by Ranbaxy Pharmaceuticals Canada Inc.

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