PRODUCT MONOGRAPH

[Pr]ratio-AMLODIPINE

Amlodipine besylate tablets

5 mg and 10 mg Amlodipine

Antihypertensive-Antianginal Agent

ratiopharm inc.
Canada, J7J 1P3

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Control # 089371, 102485 & 102486

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	tablet 5 mg, 10 mg	Lactose For a complete listing see Dosage Forms, Composition and Packaging section.

INDICATIONS AND CLINICAL USE

Hypertension:
ratio-AMLODIPINE (amlodipine besylate) is indicated in the treatment of mild to moderate essential hypyertension.

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:
ratio-AMLODIPINE (amlodipine besylate) 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.

Amlodipine besylate may be tried in combination with beta-blockers in chromic 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.

Pediatrics:

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

Geriatrics (≥ 65 years of age):

In elderly patients (≥65 years) clearance of amlodipine is decreased with a resulting increase in AUC (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism**). 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. ratio-AMLODIPINE should be used cautiously in elderly patients. Dosage adjustment is advisable (see **DOSAGE AND ADMINISTRATION**).

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredients in the formulation or component of the container. For a completed listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the product monograph.

- ratio-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).

WARNINGS AND PRECAUTIONS

Cardiovascular:

Increased Angina and/or Mycoardial 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)

ratio-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 amlodipine besylate 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

ratio-AMLODIPINE (amlodipine besylate) 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.

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 and Metabolism**). ratio-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).**

Beta-blocker Withdrawal:

ratio-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.

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.

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 is no clinical experience with amlodipine besylate in pregnant women. ratio-AMLODIPINE should be used during pregnancy only if the potential benefit outweighs the potential risk to the mother and fetus.

Nursing Mothers

It is not known whether amlodipine is excreted in human milk. Since amlodipine safety in newborns has not been established, ratio-AMLODIPINE should not be given to nursing mothers.

Pediatrics

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

Geriatrics (≥ 65 years of age)

In elderly patients (≥65 years) clearance of amlodipine is decreased with a resulting increase in AUC (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism**). 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. ratio-AMLODIPINE should be used cautiously in elderly patients. Dosage adjustment is advisable (see **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS

Clincial 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 besylate has 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 amlodipine in controlled clinical trials, adverse effects were reported 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: edema (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: edema (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: headache (8.3%), dizziness (3.0%), paresthesia (0.5%).
Autonomic Nervous System: flushing (3.1%), increased sweating (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: edema (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: edema (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: headache (7.8%), dizziness (4.5%), paresthesia (1.0%), hypoesthesia (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: dyspnea (1.1%).
Special Senses: vision abnormal (1.3%), tinnitus (0.6%).
General: fatigue (4.8%), pain (1.0%), asthenia (1.0%).

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

Cardiovascular: arrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, hypotension, peripheral ischemia, syncope, tachycardia, postural dizziness, postural hypotension, vasculitis.
Central and Peripheral Nervous System: hypoesthesia, peripheral neuropathy, tremor, vertigo.
Gastrointestinal: anorexia, constipation, dysphagia, vomiting, gingival hyperplasia.
General: allergic reaction, asthenia [+], back pain, hot flushes, malaise, rigors, weight gain.
Musculoskeletal: arthralgia, arthrosis, myalgia.

Psychiatric: sexual dysfunction (male [+] and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization.
Respiratory: epistaxis.
Skin and Appendages: pruritus[+], rash erythematous, rash maculopapular, erythema multiforme.
Special Senses: conjunctivitis, diplopia, eye pain, tinnitus.
Urinary System: micturition frequency, micturition disorder, nocturia.
Autonomic Nervous System: dry mouth, sweating increased.
Metabolic and Nutritional: hyperglycemia, thirst.
Hemopoietic: leukopenia, purpura, thrombocytopenia.

[+]These events occurred in less than 1% in placebo controlled trials, but the incidence of these side effects was between 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. 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.

DRUG INTERACTIONS

Drug-Drug Interactions:
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 CYP3A4 isoenzyme. Co-administration 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.

Drugs known to be inhibitors of the cytochrome P450 system include: azole antifungals, cimetidine, cyclosporine, erythromycin, quinidine, terfenadine, warfarin.

Drugs known to be inducers of the cytochrome P450 system include: phenobarbital, phenytoin, rifampin.

Drugs known to be biotransformed via P450 include: benzodiazepines, flecainide, imipramine, propafenone, theophylline.

Amlodipine has a low (rate of first-pass) 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, Cyclosporin, Digoxin

Pharmacokinetic interaction studies with amlodipine in healthy volunteers have indicated:

- **cimetidine** did not alter the pharmacokinetics of amlodipine.
- amlodipine did not change **warfarin**-induced prothrombin response time.
- amlodipine does not significantly alter the pharmacokinetics of **cyclosporin**.
- amlodipine did not change serum **digoxin** levels or **digoxin** renal clearance.

Antacids

Concomitant administration of Maalox® (magnesium hydroxide and aluminum hydroxide) had no effect on the disposition of a single 5 mg dose of amlodipine in 24 subjects.

Beta-blockers

When beta-adrenergic receptor blocking drugs are administered concomitantly with ratio-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

A single 100 mg dose of sildenafil (VIAGRA®) in subjects with essential hypertension had no effect on AUC_t or C_{max} 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.

Special Studies: Effect of amlodipine on other agents

Atorvastatin

In healthy volunteers, co-administration of multiple 10 mg doses of amlodipine besylate with 80 mg of atorvastatin resulted in no significant change in the AUC_t or C_{max} or T_{max} of atorvastatin.

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. Following oral administration of 10 mg amlodipine to 20 male volunteers, pharmacokinetics of amlodipine were similar when amlodipine was administered with and without grapefruit juice (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism**).

Drug-Herb Interactions:
Information is not available.

Drug-Laboratory Interactions:
Information is not available.

DOSAGE AND ADMINISTRATION

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

For both hypertension and angina, the recommended initial dose of ratio-AMLODIPINE (amlodipine besylate) is 5 mg once daily. If necessary, dose can be increased after 1 to 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 **PRECAUTIONS**).

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

Use in Children
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 **ACTIONS 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 besylate is limited. When amlodipine was ingested at doses of 105 to 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 hours after ingestion and on subsequent observation (overnight) no sequelae were noted.

Treatment:

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 ratio-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 case.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action:

ratio-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-hour dose interval with minimal peak to trough differences in blood pressure reduction. 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 2.5 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 CYP3A4 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. Elimination from the plasma is biphasic with a terminal elimination half-life of about 35 to 50 hours. Steady-state plasma levels of amlodipine are reached after 7 to 8 days of consecutive daily dosing.

Special Populations and Conditions:

Pediatrics

Two studies were conducted to evaluate the use of amlodipine in a pediatric population. In one study (pharmacokinetic), sixty-two hypertensive patients aged greater than 6 years received doses of amlodipine between 1.25mg 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 (Ka) 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}).

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%.

Gender

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).

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 hours in young normal subjects to 56 hours in the elderly patients with hepatic insufficiency.

Renal Insufficiency

The pharmacokinetics of amlodipine are 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.

Grapefruit juice

Following oral administration of 10 mg amlodipine to 20 male volunteers, pharmacokinetics of amlodipine were similar when amlodipine was administered with and without grapefruit juice. Geometric mean C_{max} 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 T_{max} of amlodipine was 7.6 hours with grapefruit juice and 7.9 hours with water. 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.

STORAGE AND STABILITY

ratio-AMLODIPINE Tablets should be stored between 15 - 30°C in tightly closed light resistance containers. Protect from humidity.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage forms and Packaging

ratio-AMLODIPINE is supplied as white, octagonal tablets: 5 mg -scored and engraved rph one side and A72 on the other; 10 mg - engraved rph on one side and A71 on the other.

ratio-AMLODIPINE is available in HDPE bottles with orange plastic caps in a package size of 100 tablets.

Composition

ratio-AMLODIPINE tablets contain amlodipine besylate equivalent to 5 and 10 mg of amlodipine per tablet.

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

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

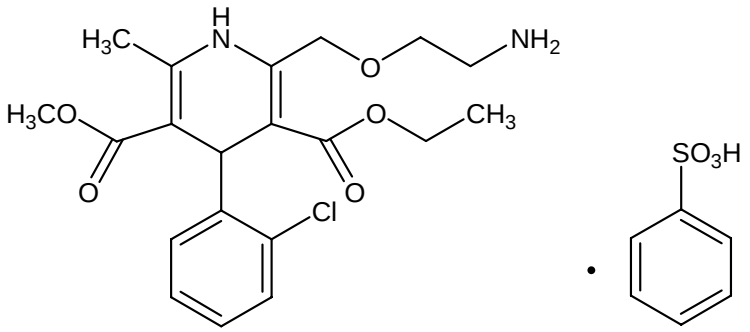
Drug Substance

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

Molecular formula and molecular mass: $C_{20}H_{25}ClN_2O_5.C_6H_6O_3S$, 567.1

Structural formula:



Physicochemical properties: Amlodipine besylate is a white crystalline substance, slightly soluble in water and sparingly soluble in ethanol.

M.p. = 203°C with decomposition

pKa = 9.02 at 23.5°C

CLINICAL TRIALS

A randomized, single-dose, 2-way crossover comparative bioavailability study of amlodipine besylate 10 mg tablets in health male volunteers was performed in the fasted state. Results are tabulated below.

Table 1: Summary Table of the Comparative Bioavailability Study

Summary Table of the Comparative Bioavailability Study **Amlodipine Besylate (Dose: 1 x 10 mg amlodipine tablet in the fasting state)** **From measured data** Geometric Mean Arithmetic Mean (CV%)				
Parameter[¶]	Test ratio-AMLODIPINE	Reference Norvasc®**	Ratio of Geometric Means (%)	90% Confidence Limits
AUC_{0-72h} (pg.h/mL)	178452.98 182907.41 (24.46)	183067.18 187826.45 (24.55)	97.48	89.41 - 106.28
C_{max} (pg/mL)	5243.85 5349.39 (18.43)	5388.61 5493.94 (19.90)	97.31	90.86 - 104.22
T_{max}[†] (h)	6.11 (22.37)	7.06 (20.32)	---	---

[¶]Due to the nature of the active ingredient (long half-life) and the design of the study, AUC_{Inf} and $T_{1/2}$ could not be accurately estimated; therefore, they are not reported.
[†]expressed as arithmetic mean (CV%) only.
**Norvasc® is manufactured by Pfizer Canada Inc. and was purchased in Canada.

Conclusion:

The relative geometric mean of the ratio-AMLODIPINE to the Canadian Reference Product (CRP), Norvasc®, formulation for C_{max} was within 80 and 125% for both the measured and the potency-corrected data. The 90% confidence interval of the relative geometric mean of the ratio-AMLODIPINE to the CRP formulation for AUC_{0-72h} was within the acceptance range of 80 - 125% for both the measured and the potency corrected data. Therefore, the ratio-AMLODIPINE

10 mg tablet formulation is judged to be bioequivalent to the Canadian Reference Product formulation, Norvasc® 10 mg tablets, on the basis of C_{max} and AUC parameters under fasting conditions.

DETAILED PHARMACOLOGY

Animal

a. Mechanism of Action Studies - *In Vitro*

Amlodipine inhibited both calcium-induced and potassium-depolarization-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 vasodilation. 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 24 h.

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 vasodilator (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.

Species	Route	Dose base mg/kg/day	Animal per dose level	Duration	Findings
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.
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 7mg/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 zona glomerulosa at 5 and 10 mg/kg/day.

Species	Route	Dose base mg/kg/day	Animal per dose level	Duration	Findings
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 zona glomerulosa of the adrenals (18 and 7 mg/kg).
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, bardycardia, 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. gastro-intestinal 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.

Species	Route	Dose base mg/kg/day	Animal per dose level	Duration	Findings
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 Metabolic Activation (MA) with Hepatic Microsomes	*salmonella typhimurium:* 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
In-vivo Cytogenetic Tests	mouse bone marrow	20 mg/kg single dose 10 mg/kg/day for 5 days	*In-vivo* p.o. s.c.	No indication of chromosome breakage or mutagenicity observed.
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/mL of culture medium With metabolic activation: 1.0 to 25 µg/mL of culture medium.	*In-vitro*	Non-activation: No evidence of induced chromosome breakage observed at levels of 1.0 µg/mL and below. At levels higher than 1.0 µg/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 typhimurium:* Strains 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. F_1 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
ratio-AMLODIPINE
Amlodipine Besylate Tablets

This leaflet is part III of a three-part "Product Monograph" published when ratio-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 ratio-AMLODIPINE. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What this medication is used for:

- ratio-AMLODIPINE (amlodipine besylate) is used for high blood pressure
- ratio-AMLODIPINE (amlodipine besylate) is used for chest pain (chronic stable angina).

What is does:

Amlodipine relaxes the blood vessels which helps to lower blood pressure and relieve chest pain.

When it should not be used:

- If you have had an allergic reaction to amlodipine besylate or to any of the non-medicinal ingredients in this product.
- If you have ever had an allergic reaction to a similar type of medicine.
- If you have very low blood pressure (less than 90 mmHg).

What the medicinal ingredient is:

Amlodipine Besylate

What the important non-medicinal ingredients are:

Non-medicinal ingredients: calcium phosphate dibasic anhydride, magnesium stearate, microcrystalline cellulose and sodium starch glycolate.

What dosage form it comes in:

Tablets, 2.5 mg, 5 mg and 10 mg

WARNINGS AND PRECAUTIONS

BEFORE you use ratio-AMLODIPINE talk to your doctor or pharmacist if you have other medical problems or conditions described below:

- hypertensive crisis or heart attack
- arterial stenosis (narrowing of the heart valve)
- liver disease
- heart failure
- low blood pressure
- pregnant or plan to become pregnant
- breast feeding

ratio-AMLODIPINE is not recommended in children less than 6 years of age.

ratio-AMLODIPINE should be used cautiously in the elderly.

INTERACTIONS WITH THIS MEDICATION

Always tell your doctor, nurse or pharmacist if you are taking any other medicines, either prescription, over-the-counter or herbal medicines, because taking some medicines together can be harmful.

Be sure to tell your doctor if you are taking or consuming: antifungals, benzodiazepines, beta-blockers, cyclosporine, erythromycin, flecainide, grapefruit juice, imipramine, phenobarbital, phenytoin, propafenone, quinidine, sildenafil, rifampin, terfenadine, theophylline.

PROPER USE OF THIS MEDICATION

Usual Dose:

Your dosage may be adjusted depending on your tolerance and responsiveness.

For both hypertension and angina, the recommended initial dose of ratio-AMLODIPINE (amlodipine besylate) is 5 mg once daily. Take ratio-AMLODIPINE as instructed by your doctor.

Overdose:

If you have taken more medication than you have been told, contact either your doctor, hospital emergency department, or nearest poison control centre immediately, even if you do not feel sick.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

As with all medications you may experience side effects while taking ratio-AMLODIPINE.

Some common side effects you may experience include: edema (swelling), headaches, palpitations, dizziness, flushing, sleepiness, nausea, abdominal pain, fatigue, rashes,

muscle cramps, tingling sensation, indigestion, diarrhea, flatulence, difficulty breathing, abnormal vision, general pain, and loss of strength.

Some uncommon side effects you may experience include: palpitations (irregular heart beat, rapid or slow heart beat), low blood pressure, fainting, lightheadedness, lightheadedness when standing, itching, increased sweating, dry mouth, constipation, insomnia, nervousness, ringing in the ear, decreased sense of touch, muscle weakness, pain or numbness, tremor, vertigo, anorexia, difficulty swallowing, vomiting, swollen gums, allergic reactions, back pain, malaise, chills, weight gain, painful joints, sexual dysfunction, depression, abnormal dreams, anxiety, depersonalization, nosebleeds, skin redness or rashes, skin lesions or blisters, double vision, eye irritation or pain, increased frequency of urination, irregular urination, urination at night, and thirst.

Very rare side effects include: heart failure, jaundice (yellowing of the skin), dry skin, severe skin reactions, hair loss, twitching, incoordination, muscle tension, migraine, apathy, loss of memory, stomach aches, abdominal pain, increased appetite, coughing, nasal congestion and sneezing, change of smell and taste, and dry eyes.

Consult your doctor if you experience these or other side effects.

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

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Edema (swelling)		✓	
	Sleepiness	✓		
	Light-headedness	✓		
	Light-headedness when standing	✓		
	Tingling sensation	✓		
	Abnormal vision		✓	

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

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Uncommon	Palpitations		✓	
	Low blood pressure		✓	
	Fainting			✓
	Mood changes	✓		
	Breathing Difficulty		✓	
	Severe skin reactions (redness, blistering, rashes)			✓
	Muscle cramps	✓		
	Nose bleeds	✓		
	Eye irritation or pain	✓		
Very rare	Allergic reactions (swelling of the tongue and face, difficulty breathing)			✓
	Yellowing of the skin			✓

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

HOW TO STORE IT

ratio-AMLODIPINE Tablets should be stored between 15 - 30°C in tightly closed light resistance containers. Protect from humidity.

Keep out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345
toll-free fax 866-678-6789
By email: cadrmp@hc-sc.gc.ca

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your doctor or pharmacist.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals obtained by contacting the sponsor, ratiopharm inc., at: 1-800-337-2584

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