PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr] RIVA-AMLODIPINE

Amlodipine Besylate Tablets

Tablets, 2.5 mg, 5 mg and 10 mg amlodipine (as amlodipine besylate), Oral

USP

Antihypertensive-Antianginal Agent

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Date of Initial Authorization:

SEP 29, 2009

Date of Revision:

DEC 17, 2025

Submission Control Number: 300825

RECENT MAJOR LABEL CHANGES

None at the time of most recent authorization	

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1. INDICATIONS

RIVA-AMLODIPINE (amlodipine besylate tablets) is indicated for:

- **Hypertension**

  RIVA-AMLODIPINE 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**

  RIVA-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.

  RIVA-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.

1.1 Pediatrics

Pediatrics (6 – 17 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of amlodipine besylate in pediatric patients has been established. Therefore, Health Canada has authorized an indication for pediatric use (see 4.2 Recommended Dose and Dosage Adjustment; 7.1.3 Pediatrics; 10.2 Pharmacodynamics).

The use of RIVA-AMLODIPINE in children less than 6 years of age is not recommended (see 7.1.3 Pediatrics).

1.2 Geriatrics

Geriatrics (> 65 years of age): Evidence from clinical studies suggests that use in the geriatric population is associated with differences in safety and exposure (see 7.1.4 Geriatrics; 10.3 Pharmacokinetics; and 4.2 Recommended Dose and Dosage Adjustment).

2. CONTRAINDICATIONS

RIVA-AMLODIPINE is contraindicated in patients:

- who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- who are hypersensitive to other dihydropyridines. Amlodipine besylate is a dihydropyridine calcium channel blocker.
- who are breast-feeding (see 7.1.2 Breast-feeding)
- with severe hypotension (less than 90 mmHg systolic)
- with shock including cardiogenic shock
- with obstruction of the outflow tract of the left ventricle (e.g., high-grade aortic stenosis)
- with hemodynamically unstable heart failure after acute myocardial infarction

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

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

4.2 Recommended Dose and Dosage Adjustment

- For both hypertension and angina, the recommended initial dose of RIVA-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 7.1.4 Geriatrics).
- **Use in Patients with Impaired Hepatic Function:** Dosage requirements have not been established in patients with impaired hepatic function. When RIVA-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 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).
- **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 7.1.3 Pediatrics; 10.2 Pharmacodynamics).

4.4 Administration

RIVA-AMLODIPINE can be administered once daily, at any time of the day, with or without food.

4.5 Missed Dose

The patient should be advised that if they miss a dose, it should be taken immediately unless it has been more than 12 hours since the missed dose. In such an event, the patient should wait for the next scheduled dose and continue on the regular schedule. A double dose should not be taken to make up for a missed dose.

5 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. In healthy volunteers, the use of charcoal up to 2 hours after administration of amlodipine 10 mg has been shown to reduce the absorption rate of amlodipine. 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: 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 besylate 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.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength / Composition	All Non-Medicinal Ingredients
Oral	Tablet / 2.5 mg, 5 mg & 10 mg	Dibasic Calcium Phosphate Anhydrous, Magnesium Stearate, Microcrystalline Cellulose, Sodium Starch Glycolate

Tablets

2.5 mg: Each white, octagonal tablet debossed with "2.5" on one side and plain on the other side contains 2.5 mg of amlodipine, as amlodipine besylate. Available in HDPE bottles of 100 and 500 tablets.

5 mg: Each white, octagonal tablet debossed with "5" and "A" on either side of the score line and plain on the reverse side contains 5 mg of amlodipine, as amlodipine besylate. Available in HDPE bottles of 100, 500 and 2000 tablets.

10 mg: Each white, octagonal tablet debossed with "10" on one side and plain on the other side contains 10 mg of amlodipine, as amlodipine besylate. Available in HDPE bottles of 100, 500 and 1000 tablets.

7 WARNINGS AND PRECAUTIONS

General

Beta-blocker Withdrawal: RIVA-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.

Concomitant Use with Strong Inhibitors of CYP 3A4: Use of RIVA-AMLODIPINE with drugs that result in strong inhibition of CYP 3A4, such as ketoconazole, clarithromycin, ritonavir, may lead to increased plasma levels of amlodipine and associated serious events (see 9.4 Drug-Drug Interactions). Such concomitant use should be avoided.

An observational study demonstrated an increased risk of hospitalization with acute kidney injury when amlodipine was used concomitantly with clarithromycin in elderly patients (> 65 years of age) compared to when it was used concomitantly with azithromycin, odds ratio [amlodipine: 1.61 (95% C.I. 1.29 – 2.02)].

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.

Use in Patients with Congestive Heart Failure: Although 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.

Of note, in an amlodipine long-term, placebo-controlled study in patients with severe heart failure (NYHA class III and IV), the reported incidence of pulmonary edema was higher in the amlodipine-treated group than in the placebo group. Calcium channel blockers, including amlodipine, may increase the risk of future cardiovascular events and mortality.

Hypotension: RIVA-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 8.2 Clinical Trial 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 10.3 Pharmacokinetics). RIVA-AMLODIPINE should, therefore, be administered with caution in these patients and careful monitoring should be performed. A lower starting dose may be required (see 4.2 Recommended Dose and Dosage Adjustment).

Patients with Severe Hepatic Impairment or Hepatic Failure: Because amlodipine besylate 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 4.2 Recommended Dose and Dosage Adjustment). Slow dose titration and careful monitoring are required in patients with severe hepatic impairment.

Reproductive Health: Female and Male Potential

Fertility

Reversible biochemical changes in the head of spermatozoa have been reported in some patients treated by calcium channel blockers. Reversible adverse effects on male rat fertility have also been suggested (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology).

7.1 Special Populations

7.1.1 Pregnant Women

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

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 labour. There was no effect on the fertility of rats treated with amlodipine.

7.1.2 Breast-feeding

In human study, the mean maternal daily dose of amlodipine was 6.0 mg and the median plasma and milk concentrations of amlodipine were 15.5 and 11.5 ng/mL, respectively, with a median milk/plasma concentration ratio of 0.85. Since amlodipine safety in newborns has not been established, RIVA-AMLODIPINE should not be given to nursing mothers. A decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother (see 2 CONTRAINDICATIONS).

7.1.3 Pediatrics

Pediatrics (6 – 17 years of age): In pediatric patients aged 6 – 17 years, safety and efficacy studies beyond 8 weeks of duration, for the treatment of hypertension, have not been conducted. The prescription in this population should be based on a careful risk/benefit assessment of the limited available information. The risk/benefit assessment should be conducted by a qualified health professional.

The use of amlodipine besylate is not recommended in patients less than 6 years of age since safety and efficacy have not been established in that population.

7.1.4 Geriatrics

Geriatrics (> 65 years of age): In elderly patients clearance of amlodipine is decreased with a resulting increase in AUC (see 10.3 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. RIVA-AMLODIPINE should be used cautiously in elderly patients. Dosage adjustment is advisable (see 4.2 Recommended Dose and Dosage Adjustment).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most serious adverse reaction associated with the amlodipine besylate is hypotension especially under gross overdose (see 5 OVERDOSAGE). The most commonly reported adverse reactions in placebo-controlled trials, that may be associated with amlodipine therapy were oedema (9.4%), headaches (8.0%), fatigue (4.5%), dizziness (3.8%) and nausea (3.4%) (see 8.2 Clinical Trial Adverse Reactions)

8.2 Clinical Trial Adverse Reactions

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 may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

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 besylate 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: 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):

Autonomic Nervous System: flushing (3.1%), hyperhidrosis (0.9%), dry mouth (0.7%).

Cardiovascular: oedema (8.9%), palpitations (2.0%), tachycardia (0.7%), postural dizziness (0.5%).

Central and Peripheral Nervous System: headaches (8.3%), dizziness (3.0%), paraesthesia (0.5%).

Gastrointestinal: nausea (2.4%), abdominal pain (1.1%), dyspepsia (0.6%), constipation (0.5%).

General: fatigue (4.1%), pain (0.5%).

Musculoskeletal: muscle cramps (0.5%).

Psychiatric: somnolence (1.4%).

Skin and Appendages: pruritus (0.7%).

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):

Autonomic Nervous System: flushing (1.9%).

Cardiovascular: oedema (9.9%), palpitations (2.0%), postural dizziness (0.6%).

Central and Peripheral Nervous System: headaches (7.8%), dizziness (4.5%), paraesthesia (1.0%), hypoesthesia (0.9%).

Gastrointestinal: nausea (4.2%), abdominal pain (2.2%), dyspepsia (1.4%), diarrhea (1.1%), flatulence (1.0%), constipation (0.9%).

General: fatigue (4.8%), pain (1.0%), asthenia (1.0%).

Musculoskeletal: muscle cramps (1.0%).

Psychiatric: somnolence (1.2%), insomnia (0.9%), nervousness (0.7%).

Respiratory System: dyspnoea (1.1%).

Skin and Appendages: rash (1.0%), pruritus (0.8%).

Special Senses: visual impairment (1.3%), tinnitus (0.6%).

8.3 Less Common Clinical Trial Adverse Reactions

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.

Autonomic Nervous System: dry mouth, hyperhidrosis.

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: hypoesthesia/paraesthesia, neuropathy peripheral, 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.

Hemopoietic: leukopenia, purpura, thrombocytopenia.

Metabolic and Nutritional: hyperglycaemia, thirst.

Musculoskeletal System: arthralgia, arthrosis, myalgia, muscle cramps.

Psychiatric: sexual dysfunction (male[+] and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization, mood altered.

Reproductive System and Breast Disorders: gynecomastia, erectile dysfunction.

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.

[+]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.

*These events were observed in marketing experience as well.

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

8.5 Post-Market Adverse Reactions

In post-marketing 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.

Post-marketing reporting has also revealed cases of extrapyramidal disorders induced by amlodipine.

9 DRUG INTERACTIONS

9.1 Serious Drug Interaction

Serious Drug Interactions
• Concomitant treatment with strong inhibitors of CYP 3A4 (see 9.4 Drug-Drug Interactions) • Concomitant treatment with clarithromycin (see 9.4 Drug-Drug Interactions)

9.2 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. 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.

9.4 Drug-Drug Interactions

Table 2: Established or Potential Drug-Drug Interactions

Proper name	Source of Evidence	Effect	Clinical comment
Atorvastatin	CT	In healthy volunteers, co-administration of multiple 10 mg doses of amlodipine besylate with 80 mg of atorvastatin resulted in no clinical significant change in the AUC (average of 18% increase) or C_{max} or T_{max} of atorvastatin.	Close monitoring is required.
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 besylate, patients should be carefully monitored since blood pressure lowering effect of beta-blockers may be augmented by amlodipine's reduction in peripheral vascular resistance.
Clarithromycin	CT	In elderly patients (> 65 years of age), concomitant use of amlodipine with clarithromycin was associated with increased risk of hospitalization with acute kidney injury.	Avoid concomitant use.

Proper name	Source of Evidence	Effect	Clinical comment
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 cyclosporin levels in renal transplant patients on amlodipine.
Dantrolene	T	In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalemia after administration of verapamil and intravenous dantrolene.	Due to risk of hyperkalemia, it is recommended that the co-administration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.
Drugs known to be biotransformed via P450 (benzodiazepines, flecainide, imipramine, propafenone, theophylline)	T	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.	
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**.**

Proper name	Source of Evidence	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 exposure of amlodipine by 22%.	These pharmacokinetic changes may be more pronounced in the elderly. Close monitoring and dose adjustment may be required.
Mechanistic Target of Rapamycin (mTOR) Inhibitors (sirolimus, temsirolimus, and everolimus)	CT T	mTOR inhibitors are CYP3A substrates. Amlodipine is a weak CYP3A inhibitor. With concomitant use of mTOR inhibitors, amlodipine may increase exposure of mTOR inhibitors.	
Sildenafil	CT	A single 100 mg dose of sildenafil in subjects with essential hypertension had no effect on AUC 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 mmHg systolic and 7 mmHg diastolic.	
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.

Proper name	Source of Evidence	Effect	Clinical comment
Strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir, clarithromycin)	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. Avoid concomitant administration of amlodipine with strong CYP3A4 inhibitors.
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

9.5 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 240 mL 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. Hence, monitoring of therapy is required.

Following oral administration of 10 mg amlodipine to 20 male volunteers, pharmacokinetics of amlodipine, 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.

9.6 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.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

RIVA-AMLODIPINE 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.

10.2 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 2.5 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.

10.3 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.

Distribution: *Ex vivo* studies have shown that approximately 93% of the circulating drug is bound to plasma proteins in hypertensive patients.

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.

Elimination: 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

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 (4.2 Recommended Dose and Dosage Adjustment). 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 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.

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 besylate 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 4.2 Recommended Dose and Dosage Adjustment). Slow dose titration and careful monitoring are required in patients with severe hepatic impairment.

11 STORAGE, STABILITY AND DISPOSAL

Store between 15°C and 30°C. Protect from light.

12 SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions for this drug product.

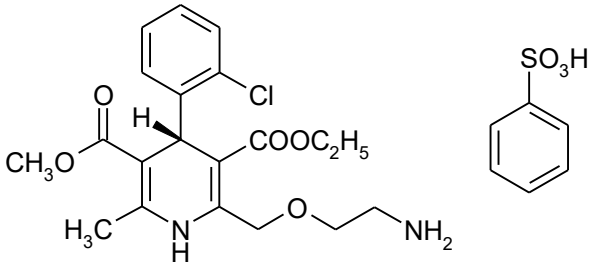
PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Amlodipine Besylate
Chemical name:	3-Ethyl 5-methyl (±)-2-[(2-aminoethoxy) methyl]-4-(o-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate monobenzenesulfonate
Molecular formula:	$C_{20}H_{25}ClN_2O_5.C_6H_6O_3S$
Molecular mass:	567.1 g/mol

Structural formula:



enantiomer

Physicochemical properties:

Description:	Amlodipine is a white or almost white powder.
Solubility:	Amlodipine is slightly soluble in water, freely soluble in methanol, and sparingly soluble in ethanol.
Melting point:	The melting range is 201ºC to 205ºC with decomposition.

14 CLINICAL TRIALS

14.2 Comparative Bioavailability Studies

A single-dose, crossover, comparative bioavailability study was performed in healthy male volunteers (n = 19) under fasting conditions on Amlodipine tablets using Laboratoire RIVA Inc. RIVA-AMLODIPINE 10 mg tablets versus the reference product, NORVASC® 10 mg Tablets, by Pfizer Canada Inc. The pharmacokinetic data calculated for the RIVA-AMLODIPINE 10 mg tablets and NORVASC® 10 mg tablets formulations are tabulated below:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Amlodipine (1 x 10 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	**RIVA-AMLODIPINE**	**NORVASC®†**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_{0-72} (ng.h/mL)	237.238 246.992 (27.6)	224.294 234.314 (29.6)	105.77	101.17 – 110.58
AUC_I (ng.h/mL)	349.389 370.719 (35.4)	341.369 361.387 (34.2)	102.35	95.25 – 109.98
C_{max} (ng/mL)	6.123 6.371 (26.2)	5.797 6.033 (27.0)	105.63	99.98 – 111.59
T_{max}[§] (h)	7.00 (5.00 – 11.00)	7.00 (5.00 – 14.00)		
$T_{½}$[€] (h)	41.83 (27.2)	45.15 (21.0)		

[†] NORVASC® was manufactured by Pfizer Canada Inc. and was purchased in Canada.
[§] Expressed as the median (range) only.
[€] Expressed as the arithmetic mean (CV %) only

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicity

Table 3: Single Dose Studies

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.

SPECIES	ROUTE	DOSE base mg/kg/day	ANIMAL PER DOSE LEVEL	DURATION	FINDINGS
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.

Table 4: Subacute and Chronic Toxicity Studies

SPECIES	ROUTE	DOSE Base mg/kg/day	ANIMAL PER DOSE LEVEL	DURATION	FINDINGS
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).

SPECIES	ROUTE	DOSE Base mg/kg/day	ANIMAL PER DOSE LEVEL	DURATION	FINDINGS
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 zona glomerulosa 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 zona glomerulosa 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 Supplementary 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.

Table 5: Mutagenicity Studies

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 1,000 mcg/mL of culture medium with metabolic activation: 1.0 to 25 mcg/mL of culture medium.	*In vitro*	Non-activation: No evidence of induced chromosome breakage observed at levels of 1.0 mcg/mL and below. At levels higher that 1.0 mcg/mL, compound produced mitotic inhibition. Activation: No drug induced clastogenic activity observed at levels up to 10 mcg/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 mcg/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.

Table 6: Reproductive and Developmental Toxicology Studies

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	24M + 24F	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.

Reproductive and Developmental Toxicology

Reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labour and decreased pup survival at dosages approximately 8 times greater than the maximum recommended dosage for humans.

Impairment of Fertility

There was no effect on the fertility of rats treated orally with amlodipine maleate (males for 64 days and females for 14 days prior to mating) at doses ≤ 10 mg amlodipine/kg/day (about 8 times the maximum recommended human dose of 10 mg/day on a mg/m2 basis, for a 50 kg human).

In another rat study in which male rats were treated with amlodipine besylate for 30 days at a dose comparable with the human dose based on mg/kg decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells.

17 SUPPORTING PRODUCT MONOGRAPHS

1. NORVASC®, tablets, 5 mg and 10 mg, submission control 277171, Product Monograph, BGP Pharma ULC, August 2, 2023.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr] RIVA-AMLODIPINE

Amlodipine Besylate Tablets

Read this carefully before you start taking **RIVA-AMLODIPINE** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **RIVA-AMLODIPINE**.

What is RIVA-AMLODIPINE used for:

RIVA-AMLODIPINE is used in adults and children 6 years of age and older to:

- Treat high blood pressure (hypertension), or
- Manage a type of chest pain called angina.

RIVA-AMLODIPINE can be used by itself or with other medicines to treat these conditions.

How does RIVA-AMLODIPINE work?

RIVA-AMLODIPINE belongs to a group of drugs called “calcium channel blocker”.

RIVA-AMLODIPINE relaxes your blood vessels, which lets your blood flow more easily and helps lower your blood pressure.

RIVA-AMLODIPINE controls chest pain by improving the supply of blood and oxygen to the heart. This reduces the amount of work that your heart has to do.

What are the ingredients in RIVA-AMLODIPINE?

Medicinal ingredients: Amlodipine besylate

Non-medicinal ingredients: Dibasic Calcium Phosphate Anhydrous, Magnesium Stearate, Microcrystalline Cellulose, Sodium Starch Glycolate

RIVA-AMLODIPINE comes in the following dosage forms:

Tablets: 2.5 mg, 5 mg and 10 mg amlodipine (as amlodipine besylate).

Do not use RIVA-AMLODIPINE if:

- You are allergic to amlodipine, or to any of the non-medicinal ingredients in RIVA-AMLODIPINE.
- You have ever had an allergic reaction to a similar type of drug.
- You have very low blood pressure (less than 90 mmHg systolic).
- You have been diagnosed with aortic stenosis (narrowing of the aortic heart valve).
- You have been diagnosed with unstable heart failure after a heart attack.
- You experience shock including cardiogenic shock.
- You are breast-feeding. Do not breast-feed while taking RIVA-AMLODIPINE.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take RIVA-AMLODIPINE. Talk about any health conditions or problems you may have, including if you:

- ever had heart or blood vessel diseases.

- have poor blood circulation in the brain.
- have liver or kidney problems.
- are pregnant, think you may be pregnant, or plan to become pregnant.
- are 65 years of age or older.

Other warnings you should know about:

Low Blood Pressure: RIVA-AMLODIPINE may occasionally cause low blood pressure (hypotension). Your healthcare professional will monitor your blood pressure, especially if you have had a stroke or take other medications to lower your blood pressure.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Serious Drug Interactions

Do not take RIVA-AMLODIPINE if you are already taking medications known as "strong inhibitors of CYP 3A4". These include:

- Clarithromycin and erythromycin (antibiotic medications)
- "Azole" drugs such as ketoconazole and itraconazole (antifungal medications)
- Ritonavir (a medication used in the treatment of HIV)

Taking RIVA-AMLODIPINE with any of these medications may cause serious drug interactions. If you are unsure if you are taking any of these medications, ask your healthcare professional.

The following may interact with RIVA-AMLODIPINE:

- Cyclosporin (used to suppress the immune system)
- Diltiazem and beta-blockers (used to lower blood pressure)
- Quinidine, flecainide and propafenone (used to treat heart rhythm problems)
- Terfenadine (an antihistamine)
- Warfarin (used to prevent blood clots)
- Sildenafil (used to treat erectile dysfunction)
- Statin drugs such as simvastatin or atorvastatin (used to treat high cholesterol)
- Tacrolimus and sirolimus (anti-rejection drugs)
- Temsirolimus and everolimus (medications used in cancer treatment)
- Dantrolene (a muscle relaxant)
- Antacids
- Benzodiazepines (a type of sedative)
- Imipramine (an antidepressant)
- Theophylline (used to treat breathing problems)
- Phenobarbital and phenytoin (used to treat seizures)
- Rifampin (an antibiotic)
- St. John's Wort
- Grapefruit. Do not eat grapefruit or drink grapefruit juice while on RIVA-AMLODIPINE.

How to take RIVA-AMLODIPINE:

- Take RIVA-AMLODIPINE exactly as your healthcare professional tells you.
- To help you remember to take your medication, try to take at the same time each day.
- Do NOT stop taking your medication without talking to your healthcare professional first.

Usual dose:

For both high blood pressure and chest pain, the usual starting dose is 5 mg once daily. If necessary, your healthcare professional may increase your dose to a maximum dose of 10 mg once daily.

Use in patients with liver disease:

The usual starting dose is 2.5 mg once daily. Your healthcare professional may increase your dose if necessary.

Use in children (6 to 17 years old):

The usual starting dose is 2.5 mg to 5 mg once daily.

Overdose:

Signs of an overdose may include:

- Prolonged low blood pressure
- Very fast heartbeat.

If you think you, or a person you are caring for, have taken too much RIVA-AMLODIPINE, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

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.

What are possible side effects from using RIVA-AMLODIPINE?

These are not all the possible side effects you may have when taking RIVA-AMLODIPINE. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- Headaches
- Tiredness, extreme sleepiness, insomnia
- Stomach pain, nausea
- Dizziness
- Flushing of the face
- Constipation, diarrhea, indigestion
- Muscle cramps
- Weak muscles
- Nervousness
- Shortness of breath

Serious side effects and what to do about them			
Frequency/Side Effect/Symptom	**Talk to your healthcare professional**		**Stop taking this drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Edema: Unusual swelling of the arms, hands, legs, feet or ankles, face or airway passages	✓		
UNCOMMON			
Allergic Reactions: Rash, hives, swelling of the face, lips, tongue or throat, difficulty breathing or swallowing, wheezing, nausea and throwing up			✓
Arrhythmia: (abnormal heart rhythms)**:** Rapid, slow or irregular heartbeat		✓	
Erectile Dysfunction (problems getting or keeping an erection)		✓	
Gynecomastia (enlargement of breast tissue in men)		✓	
Hypotension (low blood pressure)**:** Dizziness, fainting, light-headedness, blurred vision, nausea, vomiting (may occur when you go from lying or sitting to standing up)	✓		
Liver Disorder: Yellowing of the skin or eyes, dark urine and pale stools, abdominal pain, nausea, vomiting, loss of appetite		✓	
Myocardial Infarction (heart attack): pressure or squeezing pain in the chest, jaw, left arm, between the shoulder blades or upper abdomen, shortness of breath, dizziness, fatigue, light-headedness, clammy skin, sweating, indigestion, anxiety, feeling faint and possible irregular heartbeat			✓
Worsening Angina (chest pain): discomfort in the shoulder, arm, back, throat, jaw or teeth; pain or pressure in the chest		✓	
UNKNOWN FREQUENCY			
Extrapyramidal Symptoms (problems with body movement)**:** Muscle stiffness, body spasms, tremors, restlessness, upward eye rolling, exaggeration of reflexes, drooling, difficulty moving how and when you want.			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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

Storage:

Store between 15°C and 30°C. Protect from light.

Keep out of reach and sight of children.

If you want more information about RIVA-AMLODIPINE:

- Talk to your healthcare professional
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada Drug Product Database website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.labriva.com or by calling 1-800-363-7988.

This leaflet was prepared by Laboratoire RIVA Inc.

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Last revised: DEC 17, 2025