NORLIQVA- amlodipine solution
CMP Pharma, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use NORLIQVA safely and effectively. See full prescribing information for NORLIQVA.

NORLIQVA® (amlodipine) oral solution
Initial U.S. Approval: 1992

INDICATIONS AND USAGE

NORLIQVA is a calcium channel blocker for the treatment of:

- Hypertension (1.1)
  - NORLIQVA is indicated for the treatment of hypertension in adults and children 6 years of age and older, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions.
- Coronary Artery Disease (1.2)
  - Chronic Stable Angina
  - Vasospastic Angina (Prinzmetal's or Variant Angina)
  - Angiographically Documented Coronary Artery Disease in patients without heart failure or an ejection fraction <40%

DOSAGE AND ADMINISTRATION

- Adult recommended starting dose: 5 mg orally once daily with a maximum of 10 mg orally once daily. (2.1)
  - Small, fragile, or elderly patients, or patients with hepatic insufficiency may be started on 2.5 mg orally once daily. (2.1)
- Pediatric starting dose: 2.5 mg to 5 mg orally once daily. (2.2)

DOSAGE FORMS AND STRENGTHS

- Oral solution: 1 mg/mL (3)

CONTRAINDICATIONS

- Sensitivity to amlodipine (4)

WARNINGS AND PRECAUTIONS

- Symptomatic hypotension is possible, particularly in patients with severe aortic stenosis. However, acute hypotension is unlikely. (5.1)
- Worsening angina and acute myocardial infarction can develop after starting or increasing the dose of NORLIQVA, particularly in patients with severe obstructive coronary artery disease. (5.2)
- Titrate slowly in patients with severe hepatic impairment. (5.3)

ADVERSE REACTIONS

Most common adverse reactions to amlodipine were edema, dizziness, flushing and palpitation which occurred in a dose related manner. Other adverse reactions not clearly dose-related but reported with an incidence >1.0% are fatigue and nausea. (6)
To report SUSPECTED ADVERSE REACTIONS, contact CMP Pharma, Inc. at 1-844-321-1443 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- Do not exceed doses greater than 20 mg daily of simvastatin. (7.2)

USE IN SPECIFIC POPULATIONS

- Pediatric: Effect on patients less than 6 years old is not known. (8.4)
- Geriatric: Start dosing at the low end of the dose range. (8.5)
- Hepatic Impairment: Start dosing at the low end of the dose range. (8.6)

Revised: 2/2026

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Hypertension

NORLIQVA® is indicated for the treatment of hypertension, to lower blood pressure in adults and children 6 years of age and older. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions. These benefits have been seen in controlled trials of antihypertensive drugs from a wide variety of pharmacologic classes including NORLIQVA.

Control of high blood pressure should be part of comprehensive cardiovascular risk management, including, as appropriate, lipid control, diabetes management, antithrombotic therapy, smoking cessation, exercise, and limited sodium intake. Many patients will require more than one drug to achieve blood pressure goals. For specific advice on goals and management, see published guidelines, such as those of the National High Blood Pressure Education Program's Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC).

Numerous antihypertensive drugs, from a variety of pharmacologic classes and with different mechanisms of action, have been shown in randomized controlled trials to reduce cardiovascular morbidity and mortality, and it can be concluded that it is blood pressure reduction, and not some other pharmacologic property of the drugs, that is largely responsible for those benefits. The largest and most consistent cardiovascular outcome benefit has been a reduction in the risk of stroke, but reductions in myocardial infarction and cardiovascular mortality also have been seen regularly.

Elevated systolic or diastolic pressure causes increased cardiovascular risk, and the absolute risk increase per mmHg is greater at higher blood pressures, so that even modest reductions of severe hypertension can provide substantial benefit. Relative risk reduction from blood pressure reduction is similar across populations with varying absolute risk, so the absolute benefit is greater in patients who are at higher risk independent of their hypertension (for example, patients with diabetes or hyperlipidemia), and such patients would be expected to benefit from more aggressive treatment to a lower blood pressure goal.

Some antihypertensive drugs have smaller blood pressure effects (as monotherapy) in black patients, and many antihypertensive drugs have additional approved indications and effects (e.g., on angina, heart failure, or diabetic kidney disease). These considerations may guide selection of therapy.

NORLIQVA may be used alone or in combination with other antihypertensive agents.

1.2 Coronary Artery Disease (CAD)

Chronic Stable Angina
NORLIQVA is indicated for the symptomatic treatment of chronic stable angina. NORLIQVA may be used alone or in combination with other antianginal agents.

Vasospastic Angina (Prinzmetal's or Variant Angina)
NORLIQVA is indicated for the treatment of confirmed or suspected vasospastic angina. NORLIQVA may be used as monotherapy or in combination with other antianginal agents.

Angiographically Documented CAD
In patients with recently documented CAD by angiography and without heart failure or an ejection fraction <40%, NORLIQVA is indicated to reduce the risk of hospitalization for angina and to reduce the risk of a coronary revascularization procedure.

2 DOSAGE AND ADMINISTRATION

2.1 Adults

The usual initial antihypertensive oral dose of NORLIQVA is 5 mg orally once daily, and the maximum dose is 10 mg orally once daily.

Small, fragile, or elderly patients, or patients with hepatic insufficiency may be started on 2.5 mg orally once daily and this dose may be used when adding NORLIQVA to other antihypertensive therapy *[see Clinical Pharmacology (12.3)]*.

Adjust dosage according to blood pressure goals. In general, wait 7 to 14 days between titration steps. Titrate more rapidly, however, if clinically warranted, provided the patient is assessed frequently.

Angina: The recommended dose for chronic stable or vasospastic angina is 5 mg to 10 mg orally once daily, with the lower dose suggested in the elderly and in patients with hepatic insufficiency. Most patients will require 10 mg orally once daily for adequate effect.

Coronary artery disease: The recommended dose range for patients with coronary artery disease is 5 mg to 10 mg orally once daily. In clinical studies, the majority of patients required 10 mg orally once daily *[see Clinical Studies (14.4)]*.

2.2 Children

The effective antihypertensive oral dose in pediatric patients ages 6 years of age and older is 2.5 mg to 5 mg orally once daily. Doses in excess of 5 mg daily have not been studied in pediatric patients *[see Clinical Pharmacology (12.4), Clinical Studies (14.1)]*.

3 DOSAGE FORMS AND STRENGTHS

Oral Solution: 1 mg/mL clear, pale straw-colored solution with a mixed berry flavor.

4 CONTRAINDICATIONS

NORLIQVA is contraindicated in patients with sensitivity to amlodipine.

5 WARNINGS AND PRECAUTIONS

5.1 Hypotension

Symptomatic hypotension is possible, particularly in patients with severe aortic stenosis. Because of the gradual onset of action, acute hypotension is unlikely.

5.2 Increased Angina or Myocardial Infarction

Worsening angina and acute myocardial infarction can develop after starting or increasing the dose of NORLIQVA, particularly in patients with severe obstructive coronary artery disease.

5.3 Patients with Hepatic Failure

Because amlodipine is extensively metabolized by the liver and the plasma elimination half-life ($t_{1/2}$) is 56 hours in patients with impaired hepatic function, titrate slowly when administering NORLIQVA to patients with severe hepatic impairment.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Amlodipine has been evaluated for safety in more than 11,000 patients in U.S. and foreign clinical trials. In general, treatment with amlodipine was well-tolerated at doses up to 10 mg daily. Most adverse reactions reported during therapy with amlodipine were of mild or moderate severity. In controlled clinical trials directly comparing amlodipine (N=1730) at doses up to 10 mg to placebo (N=1250), discontinuation of amlodipine because of adverse reactions was required in only about 1.5% of patients and was not significantly different from placebo (about 1%). The most commonly reported adverse reactions more frequent than placebo are reflected in the table below. The incidence (%) of adverse reactions that occurred in a dose-related manner are as follows:

	Amlodipine			**Placebo**
	2.5 mg N=275	**5 mg N=296**	**10 mg N=268**	**N=520**
Edema	1.8	3.0	10.8	0.6
Dizziness	1.1	3.4	3.4	1.5
Flushing	0.7	1.4	2.6	0.0
Palpitation	0.7	1.4	4.5	0.6

Other adverse reactions that were not clearly dose-related but were reported include:

	Amlodipine (%) (N=1730)	**Placebo (%) (N=1250)**
Fatigue	4.5	2.8
Nausea	2.9	1.9

For several adverse reactions that appear to be drug and dose related, there was a

greater incidence in women than men associated with amlodipine treatment as shown in the following table:

	Amlodipine		Placebo	
	Male=% (N=1218)	Female=% (N=512)	Male=% (N=914)	Female=% (N=336)
Edema	5.6	14.6	1.4	5.1
Flushing	1.5	4.5	0.3	0.9
Palpitations	1.4	3.3	0.9	0.9
Somnolence	1.3	1.6	0.8	0.3

6.2 Postmarketing Experience

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

General: gynecomastia

Hepatic: jaundice and hepatic enzyme elevations, some requiring hospitalization

Neurologic: extrapyramidal disorder

7 DRUG INTERACTIONS

7.1 Impact of Other Drugs on Amlodipine

CYP3A Inhibitors
Co-administration with CYP3A inhibitors (moderate and strong) results in increased systemic exposure to amlodipine and may require dose reduction. Monitor for symptoms of hypotension and edema when amlodipine is co-administered with CYP3A inhibitors to determine the need for dose adjustment *[see Clinical Pharmacology (12.3)]*.

CYP3A Inducers
No information is available on the quantitative effects of CYP3A inducers on amlodipine. Blood pressure should be closely monitored when amlodipine is co-administered with CYP3A inducers.

7.2 Impact of Amlodipine on Other Drugs

Simvastatin
Co-administration of simvastatin with amlodipine increases the systemic exposure of simvastatin. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily *[see Clinical Pharmacology (12.3)]*.

Immunosuppressants
Amlodipine may increase the systemic exposure of cyclosporine or tacrolimus when co-administered. Frequent monitoring of trough blood levels of cyclosporine and tacrolimus is recommended and adjust the dose when appropriate *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary:
The limited available data based on post-marketing reports with amlodipine use in pregnant women are not sufficient to inform a drug-associated risk for major birth defects and miscarriage. There are risks to the mother and fetus associated with poorly controlled hypertension in pregnancy *[see Clinical Considerations]* In animal reproduction studies, there was no evidence of adverse developmental effects when pregnant rats and rabbits were treated orally with amlodipine maleate during organogenesis at doses approximately 10 and 20-times the maximum recommended human dose (MRHD), respectively. However for rats, litter size was significantly decreased (by about 50%) and the number of intrauterine deaths was significantly increased (about 5-fold). Amlodipine has been shown to prolong both the gestation period and the duration of labor in rats at this dose *[see Data]*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%–4% and 15%–20%, respectively.

Clinical Considerations
Disease-associated maternal and/or embryo/fetal risk
Hypertension in pregnancy increases the maternal risk for pre-eclampsia, gestational diabetes, premature delivery, and delivery complications (e.g., need for cesarean section and post-partum hemorrhage). Hypertension increases the fetal risk for intrauterine growth restriction and intrauterine death. Pregnant women with hypertension should be carefully monitored and managed accordingly.

Data
Animal Data
No evidence of teratogenicity was found when pregnant rats and rabbits were treated orally with amlodipine maleate at doses up to 10 mg amlodipine/kg/day (approximately 10 and 20 times the MRHD based on body surface area, respectively) during their respective periods of major organogenesis. However for rats, litter size was significantly decreased (by about 50%) and the number of intrauterine deaths was significantly increased (about 5-fold) in rats receiving amlodipine maleate at a dose equivalent to 10 mg amlodipine/kg/day for 14 days before mating and throughout mating and gestation. Amlodipine maleate has been shown to prolong both the gestation period and the duration of labor in rats at this dose.

8.2 Lactation

Risk Summary
Limited available data from a published clinical lactation study reports that amlodipine is present in human milk at an estimated median relative infant dose of 4.2%. No adverse effects of amlodipine on the breastfed infant have been observed. There is no available information on the effects of amlodipine on milk production.

8.4 Pediatric Use

Amlodipine (2.5 to 5 mg daily) is effective in lowering blood pressure in patients 6 years of age and older *[see Clinical Studies (14.1)]*.

Effect of amlodipine on blood pressure in patients less than 6 years of age is not known.

8.5 Geriatric Use

Clinical studies of amlodipine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Elderly patients have decreased clearance of amlodipine with a resulting increase of AUC of approximately 40–60%, and a lower initial dose may be required *[see Dosage and Administration (2.1)]*.

8.6 Hepatic Impairment

Patients with hepatic impairment have reduced clearance of amlodipine with a resulting increase of AUC. A lower initial dose may be required *[see Dosage and Administration (2.1)]*.

10 OVERDOSAGE

Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia.

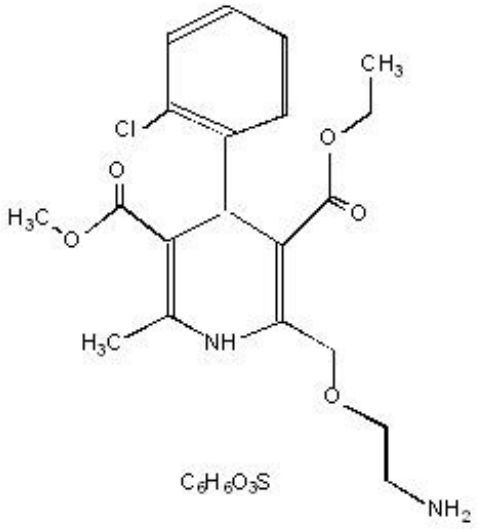
Single oral doses of amlodipine maleate equivalent to 40 mg amlodipine/kg and 100 mg amlodipine/kg in mice and rats, respectively, caused deaths. Single oral amlodipine maleate doses equivalent to 4 or more mg amlodipine/kg or higher in dogs (11 or more times the maximum recommended human dose on a mg/m^2 basis) caused a marked peripheral vasodilation and hypotension.

If massive overdose should occur, initiate active cardiac and respiratory monitoring. Frequent blood pressure measurements are essential. Should hypotension occur, provide cardiovascular support including elevation of the extremities and the judicious administration of fluids. If hypotension remains unresponsive to these conservative measures, consider administration of vasopressors (such as phenylephrine) with attention to circulating volume and urine output. As amlodipine is highly protein bound, hemodialysis is not likely to be of benefit.

11 DESCRIPTION

NORLIQVA is the besylate salt of amlodipine, a long-acting calcium channel blocker.

Amlodipine besylate is chemically described as 3-Ethyl-5-methyl (±)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate, monobenzenesulphonate. Its empirical formula is $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$, and its structural formula is:



Amlodipine besylate is a white crystalline powder with a molecular weight of 567.1. It is slightly soluble in water and sparingly soluble in ethanol. Each mL of NORLIQVA (amlodipine) oral solution contains 1 mg of amlodipine provided as 1.385 mg of amlodipine besylate and the following inactive ingredients: butylated hydroxyanisole, glycerin, propylene glycol and mixed berry flavor.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Experimental data suggest that amlodipine binds to both dihydropyridine and nondihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle 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. Negative inotropic effects can be detected *in vitro* but such effects have not been seen in intact animals at therapeutic doses. Serum calcium concentration is not affected by amlodipine. Within the physiologic pH range, amlodipine is an ionized compound (pKa=8.6), and its kinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect.

Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.

The precise mechanisms by which amlodipine relieves angina have not been fully delineated, but are thought to include the following:

Exertional Angina: In patients with exertional angina, amlodipine reduces the total peripheral resistance (afterload) against which the heart works and reduces the rate pressure product, and thus myocardial oxygen demand, at any given level of exercise.

Vasospastic Angina: Amlodipine has been demonstrated to block constriction and

restore blood flow in coronary arteries and arterioles in response to calcium, potassium epinephrine, serotonin, and thromboxane A2 analog in experimental animal models and in human coronary vessels *in vitro*. This inhibition of coronary spasm is responsible for the effectiveness of amlodipine in vasospastic (Prinzmetal's or variant) angina.

12.2 Pharmacodynamics

Hemodynamics: Following administration of therapeutic 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 a significant change in heart rate or plasma catecholamine levels with chronic dosing. Although the acute intravenous administration of amlodipine decreases arterial blood pressure and increases heart rate in hemodynamic studies of patients with chronic stable angina, chronic oral administration of amlodipine in clinical trials did not lead to clinically significant changes in heart rate or blood pressures in normotensive patients with angina.

With chronic once daily oral administration, antihypertensive effectiveness is maintained for at least 24 hours. Plasma concentrations correlate with effect in both young and elderly patients. The magnitude of reduction in blood pressure with amlodipine is also correlated with the height of pretreatment elevation; thus, individuals with moderate hypertension (diastolic pressure 105-114 mmHg) had about a 50% greater response than patients with mild hypertension (diastolic pressure 90–104 mmHg). Normotensive subjects experienced no clinically significant change in blood pressures (+1/–2 mmHg).

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 or proteinuria.

As with other calcium channel blockers, hemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with amlodipine 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 hemodynamic studies, amlodipine has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and man, even when co-administered with beta-blockers to man. Similar findings, however, have been observed in normal or well-compensated patients with heart failure with agents possessing significant negative inotropic effects.

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 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 alone, amlodipine therapy did not alter electrocardiographic intervals or produce higher degrees of AV blocks.

12.3 Pharmacokinetics

Absorption

Amlodipine reaches peak plasma concentration (C_{max}) within 6.5 hours following oral

administration of NORLIQVA. Absolute bioavailability of amlodipine has been estimated to be between 64 and 90%.

Effect of food
Administration with a high- fat, high-calorie meal did not have a significant effect on the C_{max} and AUC of NORLIQVA.

Distribution
Ex vivo studies have shown that approximately 93% of the circulating drug is bound to plasma proteins in hypertensive patients. Steady-state plasma levels of amlodipine are reached after 7 to 8 days of consecutive daily dosing.

Elimination
Metabolism
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

Excretion
Elimination from the plasma is biphasic with a mean terminal elimination half-life of 52 hours.

Specific Populations
Geriatric Patients
The renal clearance of amlodipine is lower in elderly patients compared to younger adults. This results in increase in AUC of approximately 40-60% *[see Dosage & Administration (2.1)]*.

Pediatric Patients
Sixty-two hypertensive patients aged 6 to 17 years received doses of amlodipine between 1.25 mg and 20 mg. Weight-adjusted clearance and volume of distribution were similar to values in adults.

Patients with Renal Impairment
The pharmacokinetics of amlodipine is not significantly influenced by renal impairment. Patients with renal failure may therefore receive the usual initial dose.

Patients with Hepatic Impairment
Patients with hepatic impairment have reduced clearance of amlodipine with a resulting increase in the AUC of approximately 40-60% *[see Dosage and Administration (2.1)]*.

Patients with Heart Failure
Approximately 40-60% increase in AUC was observed in patients with moderate to severe heart failure.

Drug Interaction Studies
In vitro data indicate that amlodipine has no effect on the human plasma protein binding of digoxin, phenytoin, warfarin, and indomethacin.

Impact of other drugs on amlodipine
Co-administered cimetidine, magnesium-and aluminum hydroxide antacids, sildenafil, and grapefruit juice have no impact on the exposure to amlodipine.

CYP3A inhibitors: Co-administration of a 180 mg daily dose of diltiazem with 5 mg amlodipine in elderly hypertensive patients resulted in a 60% increase in amlodipine systemic exposure. Erythromycin co-administration in healthy volunteers did not

significantly change amlodipine systemic exposure. However, strong inhibitors of CYP3A (e.g., itraconazole, clarithromycin) may increase the plasma concentrations of amlodipine to a greater extent *[see Drug Interactions (7.1)]*.

Impact of amlodipine on other drugs
Amlodipine is a weak inhibitor of CYP3A and may increase exposure to CYP3A substrates.

Co-administered amlodipine does not affect the exposure to atorvastatin, digoxin, ethanol and the warfarin prothrombin response time.

Simvastatin

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 *[see Drug Interactions (7.2)]*.

Cyclosporine

A prospective study in renal transplant patients (N=11) showed on an average of 40% increase in trough cyclosporine levels when concomitantly treated with amlodipine *[see Drug Interactions (7.2)]*.

Tacrolimus

A prospective study in healthy Chinese volunteers (N=9) with CYP3A5 expressers showed 2.5- to 4-fold the exposure to tacrolimus when concomitantly administered with amlodipine compared to tacrolimus alone. This finding was not observed in CYP3A5 non-expressers (N= 6). However, 3-fold the plasma exposure to tacrolimus was seen in a renal transplant patient (CYP3A5 non-expresser) upon initiation of amlodipine for the treatment of post-transplant hypertension. Irrespective of the CYP3A5 genotype status, the possibility of an interaction cannot be excluded with these drugs *[see Drug Interactions (7.2)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Rats and mice treated with amlodipine maleate in the diet for up to two years, at concentrations calculated to provide daily dosage levels of amlodipine 0.5, 1.25, and 2.5 mg/kg/day, showed no evidence of a carcinogenic effect of the drug. For the mouse, the highest dose was, on a mg/m^2 basis, similar to the maximum recommended human dose of 10 mg amlodipine/day.[1] For the rat, the highest dose was, on a mg/m^2 basis, about twice the maximum recommended human dose.[1]

Mutagenicity studies conducted with amlodipine maleate revealed no drug related effects at either the gene or chromosome level.

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 up to 10 mg amlodipine/kg/day (8 times the maximum recommended human dose[1] of 10 mg/day on a mg/m^2 basis).

[1] Based on patient weight of 50 kg

14 CLINICAL STUDIES

14.1 Effects in Hypertension

Adult Patients

The antihypertensive efficacy of amlodipine has been demonstrated in a total of 15 double-blind, placebo-controlled, randomized studies involving 800 patients on amlodipine and 538 on placebo. Once daily administration produced statistically significant placebo-corrected reductions in supine and standing blood pressures at 24 hours postdose, averaging about 12/6 mmHg in the standing position and 13/7 mmHg in the supine position in patients with mild to moderate hypertension. Maintenance of the blood pressure effect over the 24-hour dosing interval was observed, with little difference in peak and trough effect. Tolerance was not demonstrated in patients studied for up to 1 year. The 3 parallel, fixed dose, dose response studies showed that the reduction in supine and standing blood pressures was dose-related within the recommended dosing range. Effects on diastolic pressure were similar in young and older patients. The effect on systolic pressure was greater in older patients, perhaps because of greater baseline systolic pressure. Effects were similar in black patients and in white patients.

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 2.5 mg or 5 mg at the end of 8 weeks had significantly lower systolic 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 and 3.3 mmHg systolic on the 2.5 mg dose. Adverse events were similar to those seen in adults.

14.2 Effects in Chronic Stable Angina

The effectiveness of 5–10 mg/day of amlodipine in exercise-induced angina has been evaluated in 8 placebo-controlled, double-blind clinical trials of up to 6 weeks duration involving 1038 patients (684 amlodipine, 354 placebo) with chronic stable angina. In 5 of the 8 studies, significant increases in exercise time (bicycle or treadmill) were seen with the 10 mg dose. Increases in symptom-limited exercise time averaged 12.8% (63 sec) for amlodipine 10 mg, and averaged 7.9% (38 sec) for amlodipine 5 mg. amlodipine 10 mg also increased time to 1 mm ST segment deviation in several studies and decreased angina attack rate. The sustained efficacy of amlodipine in angina patients has been demonstrated over long-term dosing. In patients with angina, there were no clinically significant reductions in blood pressures (4/1 mmHg) or changes in heart rate (+0.3 bpm).

14.3 Effects in Vasospastic Angina

In a double-blind, placebo-controlled clinical trial of 4 weeks duration in 50 patients, amlodipine therapy decreased attacks by approximately 4/week compared with a placebo decrease of approximately 1/week ($p<0.01$). Two of 23 amlodipine and 7 of 27 placebo patients discontinued from the study due to lack of clinical improvement.

14.4 Effects in Documented Coronary Artery Disease

In PREVENT, 825 patients with angiographically documented coronary artery disease were randomized to amlodipine (5–10 mg once daily) or placebo and followed for 3 years. Although the study did not show significance on the primary objective of change in coronary luminal diameter as assessed by quantitative coronary angiography, the data suggested a favorable outcome with respect to fewer hospitalizations for angina and revascularization procedures in patients with CAD.

CAMELOT enrolled 1318 patients with CAD recently documented by angiography, without left main coronary disease and without heart failure or an ejection fraction <40%. Patients (76% males, 89% Caucasian, 93% enrolled at US sites, 89% with a history of angina, 52% without PCI, 4% with PCI and no stent, and 44% with a stent) were randomized to double-blind treatment with either amlodipine (5–10 mg once daily) or placebo in addition to standard care that included aspirin (89%), statins (83%), beta-blockers (74%), nitroglycerin (50%), anti-coagulants (40%), and diuretics (32%), but excluded other calcium channel blockers. The mean duration of follow-up was 19 months. The primary endpoint was the time to first occurrence of one of the following events: hospitalization for angina pectoris, coronary revascularization, myocardial infarction, cardiovascular death, resuscitated cardiac arrest, hospitalization for heart failure, stroke/TIA, or peripheral vascular disease. A total of 110 (16.6%) and 151 (23.1%) first events occurred in the amlodipine and placebo groups, respectively, for a hazard ratio of 0.691 (95% CI: 0.540–0.884, p = 0.003). The primary endpoint is summarized in Figure 1 below. The outcome of this study was largely derived from the prevention of hospitalizations for angina and the prevention of revascularization procedures (see Table 1). Effects in various subgroups are shown in Figure 2.

In an angiographic substudy (n=274) conducted within CAMELOT, there was no significant difference between amlodipine and placebo on the change of atheroma volume in the coronary artery as assessed by intravascular ultrasound.

Figure 1 - Kaplan-Meier Analysis of Composite Clinical Outcomes for Amlodipine versus Placebo

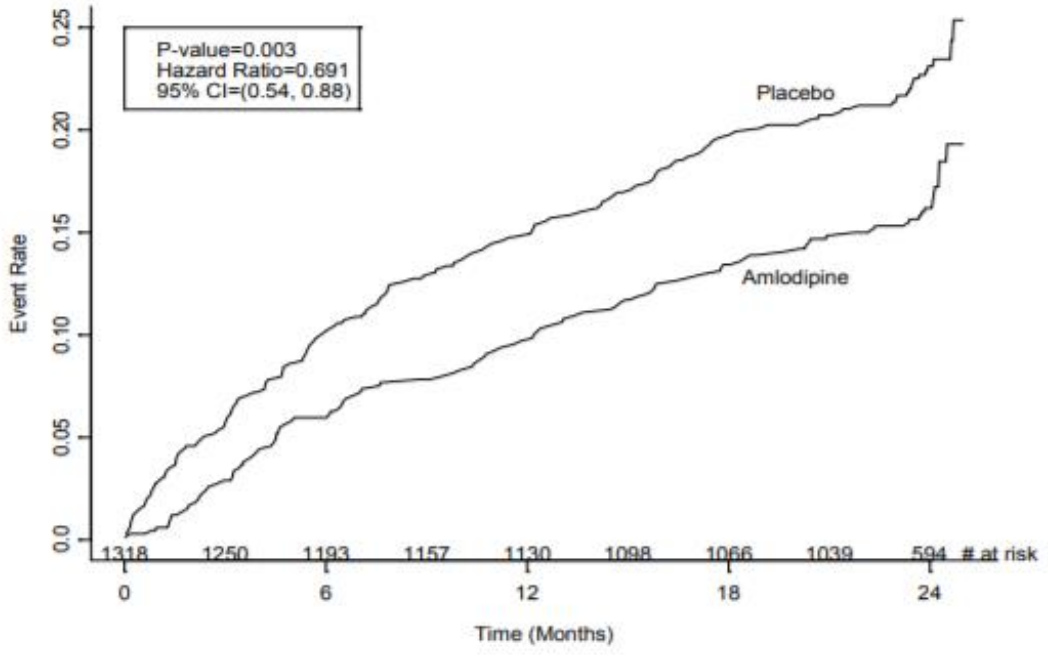
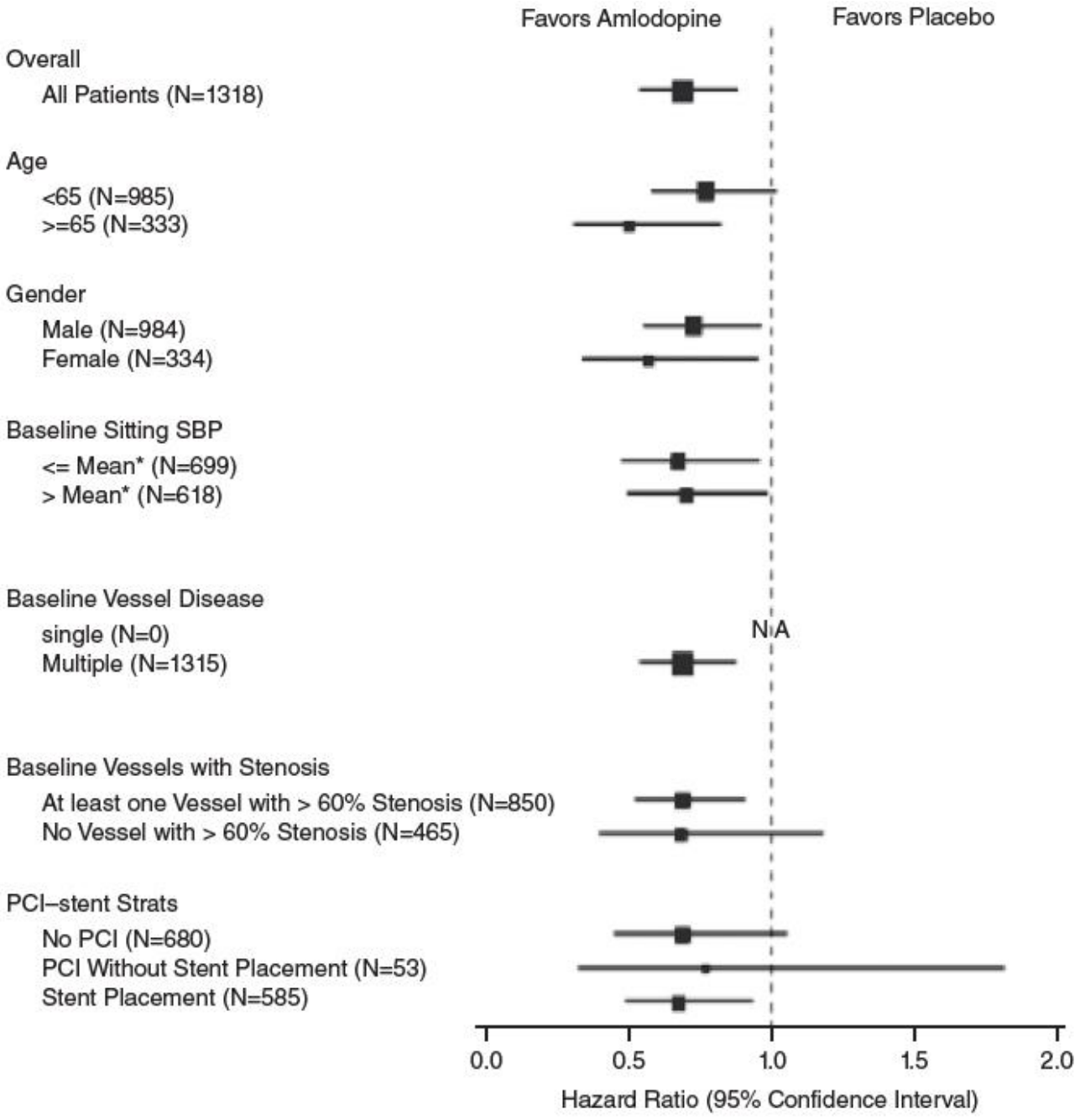


Figure 2 – Effects on Primary Endpoint of Amlodipine versus Placebo across

Sub-Groups



*The mean sitting baseline SBP is 129 mmHg

Table 1 below summarizes the significant composite endpoint and clinical outcomes from the composites of the primary endpoint. The other components of the primary endpoint including cardiovascular death, resuscitated cardiac arrest, myocardial infarction, hospitalization for heart failure, stroke/TIA, or peripheral vascular disease did not demonstrate a significant difference between amlodipine and placebo.

Table 1 – Incidence of Significant Clinical Outcomes for CAMELOT

Clinical Outcomes N (%)	Amlodipine (N=663)	Placebo (N=655)	Risk Reduction

N (%)	(N=665)	(N=655)	(p-value)
Composite CV Endpoint	**110 (16.6)**	**151 (23.1)**	**31% (0.003)**
Hospitalization for Angina*	51 (7.7)	84 (12.8)	42% (0.002)
Coronary Revascularization*	78 (11.8)	103 (15.7)	27% (0.033)

* Total patients with these events

14.5 Studies in Patients with Heart Failure

Amlodipine has been compared to placebo in four 8–12 week studies of patients with NYHA Class II/III heart failure, involving a total of 697 patients. In these studies, there was no evidence of worsened heart failure based on measures of exercise tolerance, NYHA classification, symptoms, or left ventricular ejection fraction. In a long-term (follow-up at least 6 months, mean 13.8 months) placebo-controlled mortality/morbidity study of amlodipine 5–10 mg in 1153 patients with NYHA Classes III (n=931) or IV (n=222) heart failure on stable doses of diuretics, digoxin, and ACE inhibitors, amlodipine had no effect on the primary endpoint of the study which was the combined endpoint of all-cause mortality and cardiac morbidity (as defined by life-threatening arrhythmia, acute myocardial infarction, or hospitalization for worsened heart failure), or on NYHA classification, or symptoms of heart failure. Total combined all-cause mortality and cardiac morbidity events were 222/571 (39%) for patients on amlodipine and 246/583 (42%) for patients on placebo; the cardiac morbid events represented about 25% of the endpoints in the study.

Another study (PRAISE-2) randomized patients with NYHA Class III (80%) or IV (20%) heart failure without clinical symptoms or objective evidence of underlying ischemic disease, on stable doses of ACE inhibitors (99%), digitalis (99%), and diuretics (99%), to placebo (n=827) or amlodipine (n=827) and followed them for a mean of 33 months. There was no statistically significant difference between amlodipine and placebo in the primary endpoint of all-cause mortality (95% confidence limits from 8% reduction to 29% increase on amlodipine). With amlodipine there were more reports of pulmonary edema.

16 HOW SUPPLIED/STORAGE AND HANDLING

NORLIQVA (amlodipine) oral solution, 1 mg/mL is a clear, pale straw-colored solution with a mixed berry flavor supplied in 150 mL white HDPE bottles with a child-resistant closure.

NDC 46287-037-01

Storage

Store at 20°C to 25°C (68°F to 77°F); excursion permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Dispense in light-resistant and tight (per USP) container.

Distributed by CMP Pharma, Inc., Farmville, NC 27828

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3097 R0226

Principal Display Panel - 150 mL Bottle Label

Alcohol Free

150 mL

R_x Only

NDC 46287-037-01

Norliqva®

(Amlodipine) Oral Solution
1 mg/mL

FOR ORAL USE ONLY

NORLIQVA
amlodipine solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:46287-037
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
amlodipine (UNII: 1J444QC288) (amlodipine - UNII:1J444QC288)	amlodipine	1 mg in 1 mL

Inactive Ingredients	
Ingredient Name	**Strength**
glycerin (UNII: PDC6A3C0OX)	
propylene glycol (UNII: 6DC9Q167V3)	
butylated hydroxyanisole (UNII: REK4960K2U)	

Product Characteristics			
Color		**Score**	
Shape		**Size**	
Flavor	BERRY	**Imprint Code**	
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:46287-037-01	150 mL in 1 BOTTLE; Type 0: Not a Combination Product	03/02/2026	

Marketing Information			
Marketing Category	**Application Number or Monograph Citation**	**Marketing Start Date**	**Marketing End Date**
NDA	NDA214439	03/02/2026	

Labeler - CMP Pharma, Inc. (005224175)

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