NEW DRUG APPROVAL

Brand Name	Norliqva®
Generic Name	amlodipine
Drug Manufacturer	CMP Pharma, Inc.

New Drug Approval

FDA approval date: February 24, 2022

Review designation: Standard

Type of review: Type 5 - New Formulation or New Manufacturer, New Drug Application (NDA): 214439

Dispensing restriction: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Blood pressure is the pressure of blood pushing against the walls of your arteries. Arteries carry blood from your heart to other parts of your body.

Blood pressure normally rises and falls throughout the day, but it can damage your heart and cause health problems if it stays high for a long time. Hypertension, also called high blood pressure, is blood pressure that is higher than normal.

In 2017, the American College of Cardiology and the American Heart Association published new guidelines for hypertension management and defined high hypertension as a blood pressure at or above 130/80 mmHg. Stage 2 hypertension is defined as a blood pressure at or above 140/90 mmHg.

Having hypertension puts you at risk for heart disease and stroke, which are leading causes of death in the United States. In 2019, more than half a million deaths in the United States had hypertension as a primary or contributing cause.

Nearly half of adults in the United States (47%, or 116 million) have hypertension, defined as a systolic blood pressure greater than 130 mmHg or a diastolic blood pressure greater than 80 mmHg or are taking medication for hypertension.

Only about 1 in 4 adults (24%) with hypertension have their condition under control.

About half of adults (45%) with uncontrolled hypertension have a blood pressure of 140/90 mmHg or higher. This includes 37 million U.S. adults.

About 34 million adults who are recommended to take medication may need it to be prescribed and to start taking it. Almost two out of three of this group (19 million) have a blood pressure of 140/90 mmHg or higher. High blood pressure was a primary or contributing cause of death for 516,955 people in the United States in 2019.

Coronary artery disease is a common heart condition that involves atherosclerotic plaque formation in the vessel lumen. This leads to impairment in blood flow and thus oxygen delivery to the myocardium. It is a cause of major morbidity and mortality in the US and worldwide.

It is estimated that 7.6% of men and 5.0% of women in the US lived with coronary artery disease from 2009 to 2012 based on the national health survey done by the American Heart Association (AHA). This amount to 15.5 million Americans afflicted with the disease during this time.

Efficacy

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 post dose, 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.

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. 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).

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

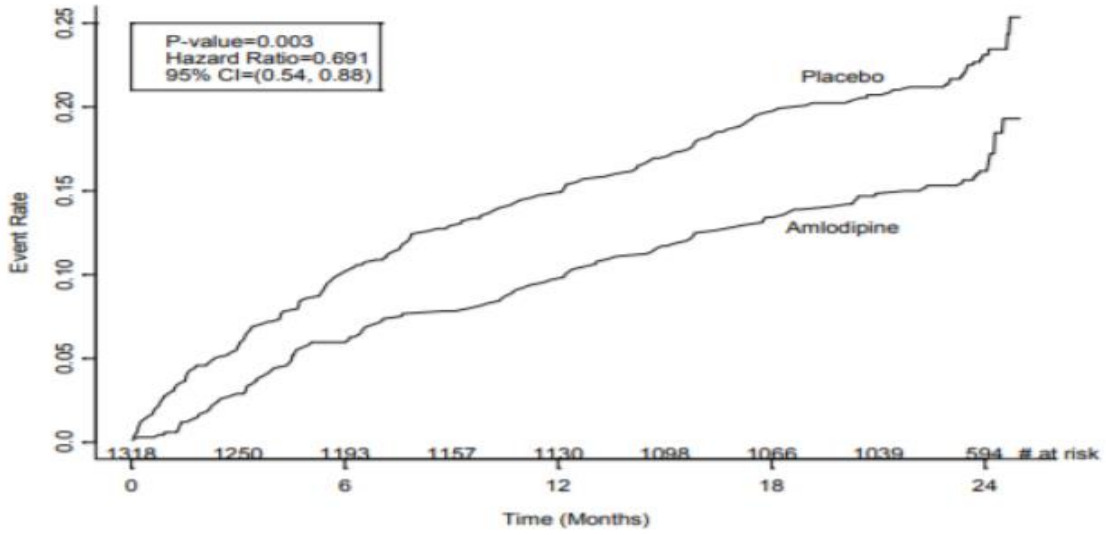
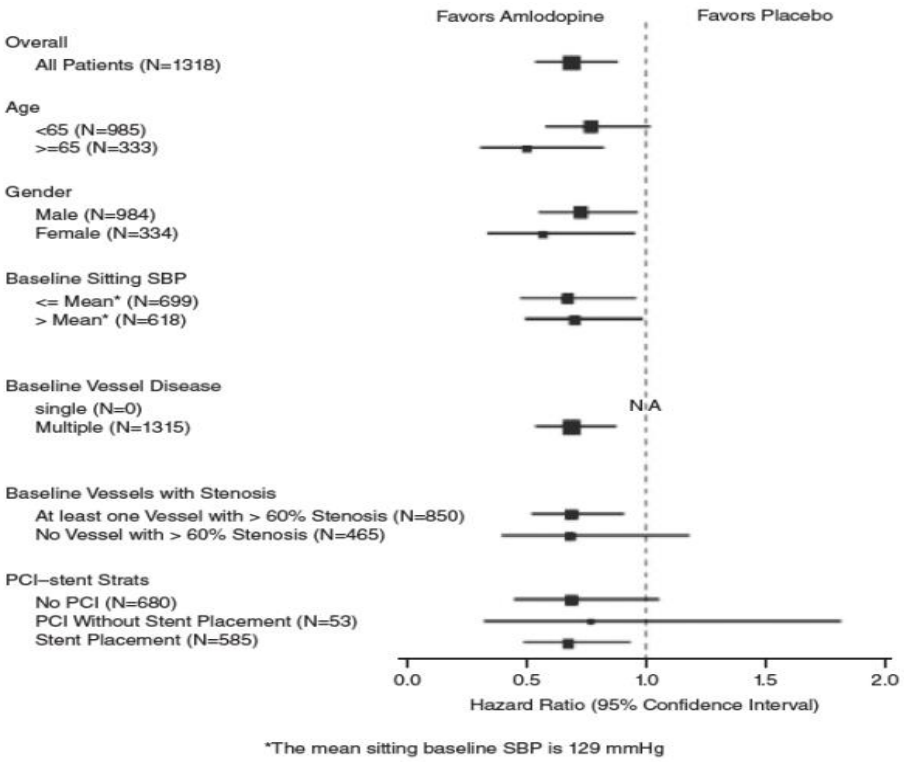


Figure 2 – Effects on Primary Endpoint of Amlodipine versus Placebo across Sub-Groups



*The mean sitting baseline SBP is 129 mmHg

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.

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 favourable 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%), anticoagulants (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).

In an angiographic sub study (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.

Tale 1 – Incidence of Significant Clinical Outcomes for CAMELOT

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

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.

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.

	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

Safety

ADVERSE EVENTS

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.

WARNINGS & PRECAUTIONS

Hypotension:

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

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.

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.

CONTRAINDICATIONS

Norliqva® is contraindicated in patients with sensitivity to amlodipine.

Clinical Pharmacology

MECHANISMS 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. 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.

Dose & Administration

ADULTS

The recommended dose range for patients with hypertension & coronary artery disease is 5 mg to 10 mg orally once daily.

PEDIATRICS

Pediatric patients ages 6 years of age and older: 2.5 mg to 5 mg orally once daily.

GERIATRICS

2.5 mg orally once daily

RENAL IMPAIRMENT

No Dosage adjustment required

HEPATIC IMPAIRMENT

2.5 mg orally once daily

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Oral solution: 1 mg/mL