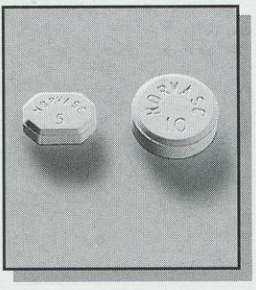
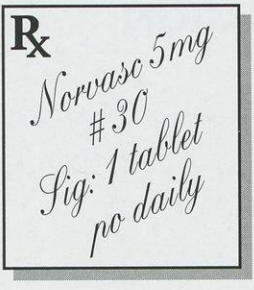
Norvasc advertisement.

[s.l.]: [s.n.], 1993

In hypertension or angina, convenient once-daily dosing

- The usual starting dose is 5 mg in hypertension or angina
  - —In hypertension, small, fragile, or elderly individuals or patients with hepatic insufficiency may be started on 2.5 mg once daily[2]
- Titration can proceed to 10 mg
  - —Most angina patients will require 10 mg
- Can be taken with or without food
- The most common side effects are headache and edema





Once-Daily

5-mg and 10-mg tablets

NORVASC®

(amlodipine besylate)

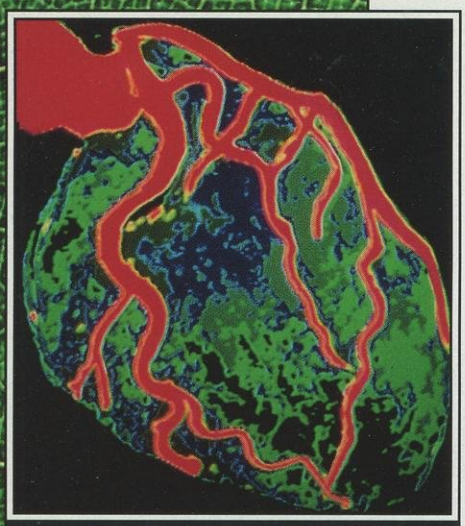
EFFICACY AND SAFETY THAT'S EASY TO LIVE WITH

References

1. Neaton JD, Grimm RH Jr, Prineas RJ, et al, for the Treatment of Mild Hypertension Study Research Group. Treatment of Mild Hypertension Study: final results. *JAMA.* 1993;270:713–724.

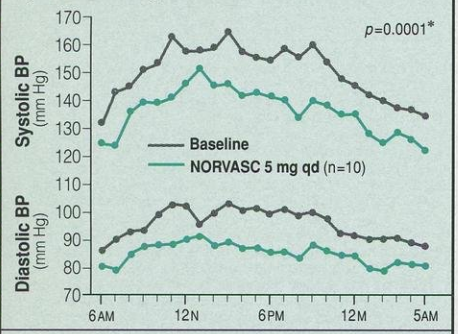
2. Data on file. Pfizer Inc, New York, NY.

Pfizer Labs • NHO • Pratt • Roerig
U.S. Pharmaceuticals Group



Digital subtraction angiography of the heart

Mean blood pressure (BP) over 24 hours (week 4 data)[3]



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*Average of mean BP values over 24 hours at week 4 versus baseline averages.

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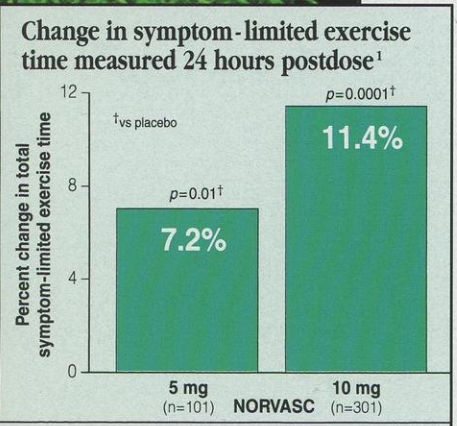

Data from eight placebo-controlled, double-blind, randomized studies of the effect of NORVASC on symptom-limited exercise time. All studies included a 2-week, single-blind, placebo run-in period. The eight studies included five monotherapy trials and three add-on therapy trials. Treatment ranged from 4 to 6 weeks. Placebo group (n=297) had a 2.1% increase in symptom-limited exercise time. Exercise time at baseline: placebo, 480 sec; 5 mg, 523 sec; 10 mg, 493 sec. (Data on file.[1])

FOR HYPERTENSION OR ANGINA

NORVASC, a calcium channel blocker, provides effective yet gentle 24-hour control with intrinsic once-daily dosing[1]

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Effective as initial therapy for mild to moderate hypertension[1]

- Over 80% of patients responding to NORVASC are controlled on 5 mg[1]
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Gradual onset of action and minimal adverse effects

- No clinically significant effects on heart rate[1] or cardiac conduction[1]; no negative inotropic effects at clinical doses in hemodynamic studies,‡ even when administered with beta blockers to humans[1]
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  - Chronic obstructive pulmonary disease, well-compensated Classes II and III congestive heart failure (CHF),§ peripheral vascular disease, diabetes mellitus, and abnormal lipid profiles[1]
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‡Similar hemodynamic findings, however, have been observed with agents possessing significant negative inotropic effects.
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ONCE-DAILY

5-mg and 10-mg tablets

NORVASC®

(amlodipine besylate)

INITIAL THERAPY IN HYPERTENSION OR ANGINA THAT CONSIDERS THE CARDIOVASCULAR ENVIRONMENT

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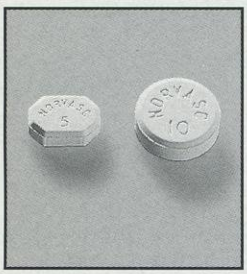

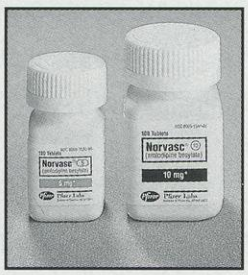

Rx
Norvasc 5mg
#30
Sig: 1 tablet daily

ONCE-DAILY NORVASC® (amlodipine besylate)

5-mg and 10-mg tablets

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Brief Summary
NORVASC® (amlodipine besylate) Tablets
For Oral Use

CONTRAINDICATIONS: NORVASC is contraindicated in patients with known sensitivity to amlodipine.

WARNINGS: 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.

PRECAUTIONS: General: Since the vasodilation induced by NORVASC is gradual in onset, acute hypotension has rarely been reported after oral administration of NORVASC. Nonetheless, caution should be exercised when administering NORVASC as with any other peripheral vasodilator particularly in patients with severe aortic stenosis.

Use in Patients with Congestive Heart Failure: Although hemodynamic studies and a controlled trial in NYHA Class II-III heart failure patients have shown that NORVASC did not lead to clinical deterioration as measured by exercise tolerance, left ventricular ejection fraction, and clinical symptomatology, studies have not been performed in patients with NYHA Class IV heart failure. In general, all calcium channel blockers should be used with caution in patients with heart failure.

Beta-Blocker Withdrawal: NORVASC is not a beta-blocker and therefore gives no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be by gradual reduction of the dose of the beta-blocker.

Patients with Hepatic Failure: Since NORVASC is extensively metabolized by the liver and the plasma elimination half-life (t ½) is 56 hours in patients with impaired hepatic function, caution should be exercised when administering NORVASC to patients with severe hepatic impairment.

Drug Interactions: *In vitro* data in human plasma indicate that NORVASC has no effect on the protein binding of drugs tested (digoxin, phenytoin, warfarin, and indomethacin). Special studies have indicated that the co-administration of NORVASC with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers; that co-administration with cimetidine did not alter the pharmacokinetics of amlodipine; and that co-administration with warfarin did not change the warfarin prothrombin response time.

In clinical trials, NORVASC has been safely administered with thiazide diuretics, beta-blockers, angiotensin converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.

Drug/Laboratory Test Interactions: None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m^2 basis), was close to the maximum tolerated dose for mice but not for rats.

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Nursing Mothers: It is not known whether amlodipine is excreted in human milk. In the absence of this information, it is recommended that nursing be discontinued while NORVASC is administered.

Pediatric Use: Safety and effectiveness of NORVASC in children have not been established.

ADVERSE REACTIONS: NORVASC has been evaluated for safety in more than 11,000 patients in U.S. and foreign clinical trials. In general, treatment with NORVASC was well-tolerated at doses up to 10 mg daily. Most adverse reactions reported during therapy with NORVASC were of mild or moderate severity. In controlled clinical trials directly comparing NORVASC (N=1730) in doses up to 10 mg to placebo (N=1250), discontinuation of NORVASC due to adverse reactions was required in only about 1.5% of patients and was not significantly different from placebo (about 1%). The most common side effects are headache and edema. The incidence (%) of side effects which occurred in a dose related manner are as follows: edema (1.8% at 2.5 mg, 3.0% at 5.0 mg, and 10.8% at 10.0 mg, compared with 0.6% placebo); dizziness (1.1% at 2.5 mg, 3.4% at 5.0 mg, and 3.4% at 10.0 mg, compared with 1.5% placebo); flushing (0.7% at 2.5 mg, 1.4% at 5.0 mg, and 2.6% at 10.0 mg, compared with 0.0% placebo); and palpitation (0.7% at 2.5 mg, 1.4% at 5.0 mg, and 4.5% at 10.0 mg, compared with 0.6% placebo).

Other adverse experiences which were not clearly dose related but which were reported with an incidence greater than 1.0% in placebo-controlled clinical trials include the following: headache (7.3%, compared with 7.8% placebo); fatigue (4.5%, compared with 2.8% placebo); nausea (2.9%, compared with 1.9% placebo); abdominal pain (1.6%, compared with 0.3% placebo); and somnolence (1.4%, compared with 0.6% placebo).

For several adverse experiences that appear to be drug and dose related, there was a greater incidence in women than men associated with amlodipine treatment as follows: edema (5.6% in men, 14.6% in women, compared with a placebo incidence in men of 1.4% and 5.1% in women); flushing (1.5% in men, 4.5% in women, compared with a placebo incidence of 0.3% in men and 0.9% in women); palpitations (1.4% in men, 3.3% in women, compared with a placebo incidence of 0.9% in men and 0.9% in women); and somnolence (1.3% in men, 1.6% in women, compared with a placebo incidence of 0.8% in men and 0.3% in women).

The following events occurred in ≤1% but >0.1% of patients in controlled clinical trials or under conditions of open trials or marketing experience where a causal relationship is uncertain; they are listed to alert the physician to a possible relationship: **cardiovascular:** arrhythmia, bradycardia, chest pain, hypotension, peripheral ischemia, syncope, tachycardia, postural dizziness, postural hypotension; **central and peripheral nervous system:** hypoesthesia, paresthesia, tremor, vertigo; **gastrointestinal:** anorexia, constipation, dyspepsia,** dysphagia, diarrhea, flatulence, vomiting; **general:** asthenia,** back pain, hot flushes, malaise, pain, rigors, weight gain; **musculo-skeletal system:** arthralgia, arthrosis, muscle cramps,** myalgia; **psychiatric:** sexual dysfunction (male** and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization; **respiratory system:** dyspnea,** epistaxis; **skin and appendages:** pruritus,** rash,** rash erythematous, rash maculopapular; **special senses:** abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus; **urinary system:** micturition frequency, micturition disorder, nocturia; **autonomic nervous system:** dry mouth, sweating increased; **metabolic and nutritional:** thirst; **hemopoietic:** purpura.

The following events occurred in ≤0.1% of patients: cardiac failure, pulse irregularity, extrasystoles, skin discoloration, urticaria, skin dryness, alopecia, dermatitis, muscle weakness, twitching, ataxia, hypertonia, migraine, cold and clammy skin, apathy, agitation, amnesia, gastritis, increased appetite, loose stools, coughing, rhinitis, dysuria, polyuria, parosmia, taste perversion, abnormal visual accommodation, and xerophthalmia.

Other reactions occurred sporadically in single patients and cannot be distinguished from concurrent disease states or medications.

NORVASC therapy has not been associated with clinically significant changes in routine laboratory tests. No clinically relevant changes were noted in serum potassium, serum glucose, total triglycerides, total cholesterol, HDL cholesterol, uric acid, blood urea nitrogen, creatinine or liver function tests.

NORVASC has been used safely in patients with chronic obstructive pulmonary disease, well compensated congestive heart failure, peripheral vascular disease, diabetes mellitus, and abnormal lipid profiles.

OVERDOSAGE: Single oral doses of 40 mg/kg and 100 mg/kg in mice and rats, respectively, caused deaths. A single oral dose of 4 mg/kg or higher in dogs caused a marked peripheral vasodilation and hypotension.

Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia. In humans, experience with intentional overdosage of NORVASC is limited. Reports of intentional overdosage include a patient who ingested 250 mg and was asymptomatic and was not hospitalized; another (120 mg) was hospitalized, underwent gastric lavage and remained normotensive; the third (105 mg) was hospitalized and had hypotension (90/50 mmHg) which normalized following plasma expansion. A patient who took 70 mg amlodipine and an unknown quantity of benzodiazepine in a suicide attempt, developed shock which was refractory to treatment and died the following day with abnormally high benzodiazepine plasma concentration. A case of accidental drug overdose has been documented in a 19 month old male who ingested 30 mg amlodipine (about 2 mg/kg). During the emergency room presentation, vital signs were stable with no evidence of hypotension, but a heart rate of 180 bpm. Ipecac was administered 3.5 hours after ingestion and on subsequent observation (overnight) no sequelae were noted.

If massive overdose should occur, active cardiac and respiratory monitoring should be instituted. Frequent blood pressure measurements are essential. Should hypotension occur, cardiovascular support including elevation of the extremities and the judicious administration of fluids should be initiated. If hypotension remains unresponsive to these conservative measures, administration of vasopressors (such as phenylephrine), should be considered with attention to circulating volume and urine output. Intravenous calcium gluconate may help to reverse the effects of calcium entry blockade. As NORVASC is highly protein bound, hemodialysis is not likely to be of benefit.

* Based on patient weight of 50 kg.
**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.

More detailed professional information available on request.
Revised August 1992

NC639A93

Pfizer Labs

ONCE-DAILY NORVASC® (amlodipine besylate)...

Hypertension or angina control

INITIAL THERAPY THAT CONSIDERS THE CARDIOVASCULAR ENVIRONMENT

Please see brief summary of prescribing information on last page of this advertisement.

NORVASC®

(amlodipine besylate)

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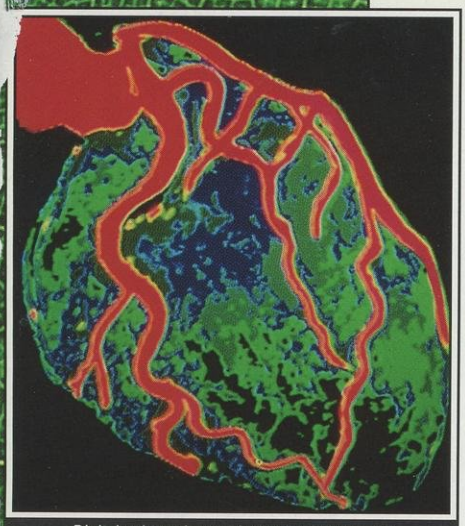

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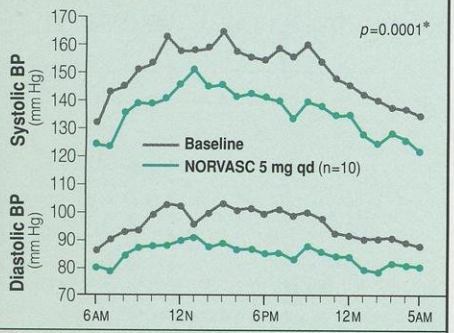

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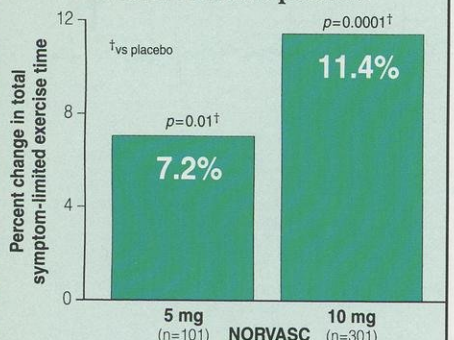

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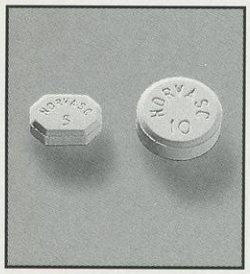

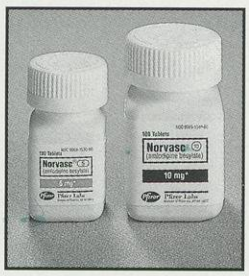

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Norvasc 5mg
#30
Sig: 1 tablet daily

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Nursing Mothers: It is not known whether amlodipine is excreted in human milk. In the absence of this information, it is recommended that nursing be discontinued while NORVASC is administered.

Pediatric Use: Safety and effectiveness of NORVASC in children have not been established.

ADVERSE REACTIONS: NORVASC has been evaluated for safety in more than 11,000 patients in U.S. and foreign clinical trials. In general, treatment with NORVASC was well-tolerated at doses up to 10 mg daily. Most adverse reactions reported during therapy with NORVASC were of mild or moderate severity. In controlled clinical trials directly comparing NORVASC (N=1730) in doses up to 10 mg to placebo (N=1250), discontinuation of NORVASC due to adverse reactions was required in only about 1.5% of patients and was not significantly different from placebo (about 1%). The most common side effects are headache and edema. The incidence (%) of side effects which occurred in a dose related manner are as follows: edema (1.8% at 2.5 mg, 3.0% at 5.0 mg, and 10.8% at 10.0 mg, compared with 0.6% placebo); dizziness (1.1% at 2.5 mg, 3.4% at 5.0 mg, and 3.4% at 10.0 mg, compared with 1.5% placebo); flushing (0.7% at 2.5 mg, 1.4% at 5.0 mg, and 2.6% at 10.0 mg, compared with 0.0% placebo); and palpitation (0.7% at 2.5 mg, 1.4% at 5.0 mg, and 4.5% at 10.0 mg, compared with 0.6% placebo).

Other adverse experiences which were not clearly dose related but which were reported with an incidence greater than 1.0% in placebo-controlled clinical trials include the following: headache (7.3%, compared with 7.8% placebo); fatigue (4.5%, compared with 2.8% placebo); nausea (2.9%, compared with 1.9% placebo); abdominal pain (1.6%, compared with 0.3% placebo); and somnolence (1.4%, compared with 0.6% placebo).

For several adverse experiences that appear to be drug and dose related, there was a greater incidence in women than men associated with amlodipine treatment as follows: edema (5.6% in men, 14.6% in women, compared with a placebo incidence in men of 1.4% and 5.1% in women); flushing (1.5% in men, 4.5% in women, compared with a placebo incidence of 0.3% in men and 0.9% in women); palpitations (1.4% in men, 3.3% in women, compared with a placebo incidence of 0.9% in men and 0.9% in women); and somnolence (1.3% in men, 1.6% in women, compared with a placebo incidence of 0.8% in men and 0.3% in women).

The following events occurred in ≤1% but >0.1% of patients in controlled clinical trials or under conditions of open trials or marketing experience where a causal relationship is uncertain; they are listed to alert the physician to a possible relationship: **cardiovascular:** arrhythmia, bradycardia, chest pain, hypotension, peripheral ischemia, syncope, tachycardia, postural dizziness, postural hypotension; **central and peripheral nervous system:** hypoesthesia, paresthesia, tremor, vertigo; **gastrointestinal:** anorexia, constipation, dyspepsia,** dysphagia, diarrhea, flatulence, vomiting; **general:** asthenia,** back pain, hot flushes, malaise, pain, rigors, weight gain; **musculo-skeletal system:** arthralgia, arthrosis, muscle cramps,** myalgia; **psychiatric:** sexual dysfunction (male** and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization; **respiratory system:** dyspnea,** epistaxis; **skin and appendages:** pruritus,** rash,** rash erythematous, rash maculopapular; **special senses:** abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus; **urinary system:** micturition frequency, micturition disorder, nocturia; **autonomic nervous system:** dry mouth, sweating increased; **metabolic and nutritional:** thirst; **hemopoietic:** purpura.

The following events occurred in ≤0.1% of patients: cardiac failure, pulse irregularity, extrasystoles, skin discoloration, urticaria, skin dryness, alopecia, dermatitis, muscle weakness, twitching, ataxia, hypertonia, migraine, cold and clammy skin, apathy, agitation, amnesia, gastritis, increased appetite, loose stools, coughing, rhinitis, dysuria, polyuria, parosmia, taste perversion, abnormal visual accommodation, and xerophthalmia.

Other reactions occurred sporadically in single patients and cannot be distinguished from concurrent disease states or medications.

NORVASC therapy has not been associated with clinically significant changes in routine laboratory tests. No clinically relevant changes were noted in serum potassium, serum glucose, total triglycerides, total cholesterol, HDL cholesterol, uric acid, blood urea nitrogen, creatinine or liver function tests.

NORVASC has been used safely in patients with chronic obstructive pulmonary disease, well compensated congestive heart failure, peripheral vascular disease, diabetes mellitus, and abnormal lipid profiles.

OVERDOSAGE: Single oral doses of 40 mg/kg and 100 mg/kg in mice and rats, respectively, caused deaths. A single oral dose of 4 mg/kg or higher in dogs caused a marked peripheral vasodilation and hypotension.

Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia. In humans, experience with intentional overdosage of NORVASC is limited. Reports of intentional overdosage include a patient who ingested 250 mg and was asymptomatic and was not hospitalized; another (120 mg) was hospitalized, underwent gastric lavage and remained normotensive; the third (105 mg) was hospitalized and had hypotension (90/50 mmHg) which normalized following plasma expansion. A patient who took 70 mg amlodipine and an unknown quantity of benzodiazepine in a suicide attempt, developed shock which was refractory to treatment and died the following day with abnormally high benzodiazepine plasma concentration. A case of accidental drug overdose has been documented in a 19 month old male who ingested 30 mg amlodipine (about 2 mg/kg). During the emergency room presentation, vital signs were stable with no evidence of hypotension, but a heart rate of 180 bpm. Ipecac was administered 3.5 hours after ingestion and on subsequent observation (overnight) no sequelae were noted.

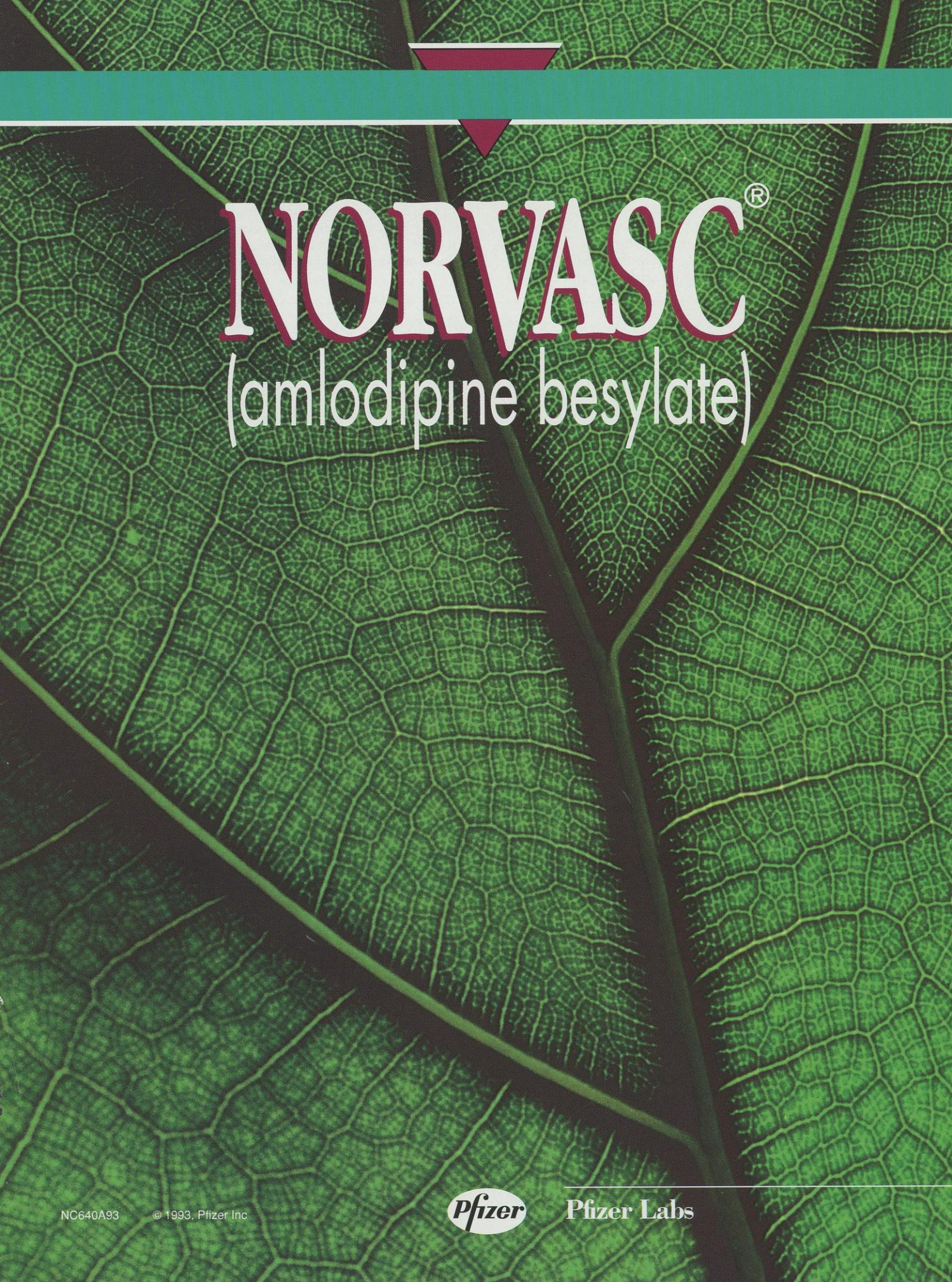
If massive overdose should occur, active cardiac and respiratory monitoring should be instituted. Frequent blood pressure measurements are essential. Should hypotension occur, cardiovascular support including elevation of the extremities and the judicious administration of fluids should be initiated. If hypotension remains unresponsive to these conservative measures, administration of vasopressors (such as phenylephrine), should be considered with attention to circulating volume and urine output. Intravenous calcium gluconate may help to reverse the effects of calcium entry blockade. As NORVASC is highly protein bound, hemodialysis is not likely to be of benefit.

* Based on patient weight of 50 kg.
**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.

More detailed professional information available on request.
Revised August 1992

NC639A93

Pfizer Labs



Pfizer Labs

NEW ONCE-DAILY NORVASC® (amlodipine besylate)...

In hypertension or angina therapy

CONSIDER THE CARDIOVASCULAR ENVIRONMENT

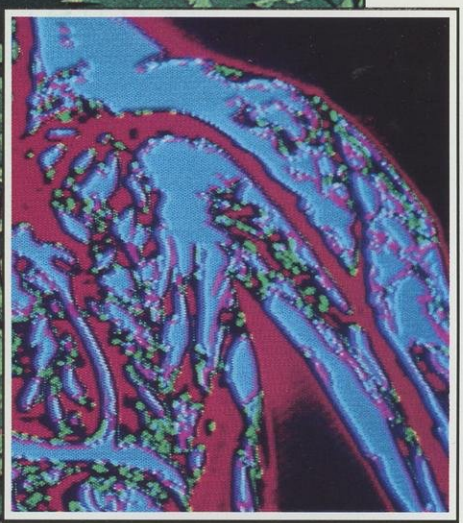
INTRODUCING ONCE-DAILY

5-mg and 10-mg tablets

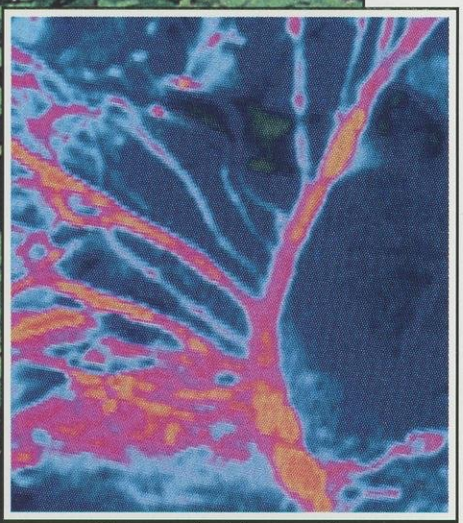
NORVASC®

(amlodipine besylate)

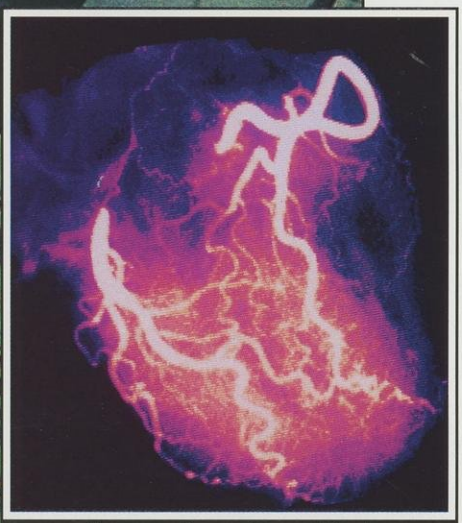
Please see brief summary of prescribing information on last page of this advertisement.



Arteriogram of peripheral vasculature



Arteriogram of peripheral vasculature



Coronary angiogram of a normal heart

Effective Treatment of Hypertension or Angina That Does Not Disturb Key Physiologic Parameters

EFFICACY

NORVASC, a new calcium channel blocker (CCB), provides effective yet gentle 24-hour control with intrinsic once-daily dosing FOR HYPERTENSION OR ANGINA[1]

SAFETY

Gradual onset of action and minimal adverse effects

- No clinically significant effects on heart rate[1]
- Neutral effect on lipids; no impairment of normal renal function
- Well tolerated: only 1.5% of patients in placebo-controlled trials (n=1730) discontinued NORVASC therapy due to adverse effects[1]
- Has been used safely in patients with concomitant diseases
  - —Chronic obstructive pulmonary disease, well-compensated Class II-III congestive heart failure (CHF),* peripheral vascular disease, diabetes mellitus, and abnormal lipid profiles[1]

*Therapy should be initiated with caution. See PRECAUTIONS section of brief summary.

DOSING

Intrinsic once-daily dosing

- The usual starting dose is 5 mg in angina or hypertension
  - —In hypertension, small, fragile, or elderly individuals or patients with hepatic insufficiency may be started on 2.5 mg once daily
- Titration can proceed to 10 mg
  - —Most angina patients will require 10 mg

NEW, ONCE-DAILY

5-mg and 10-mg tablets

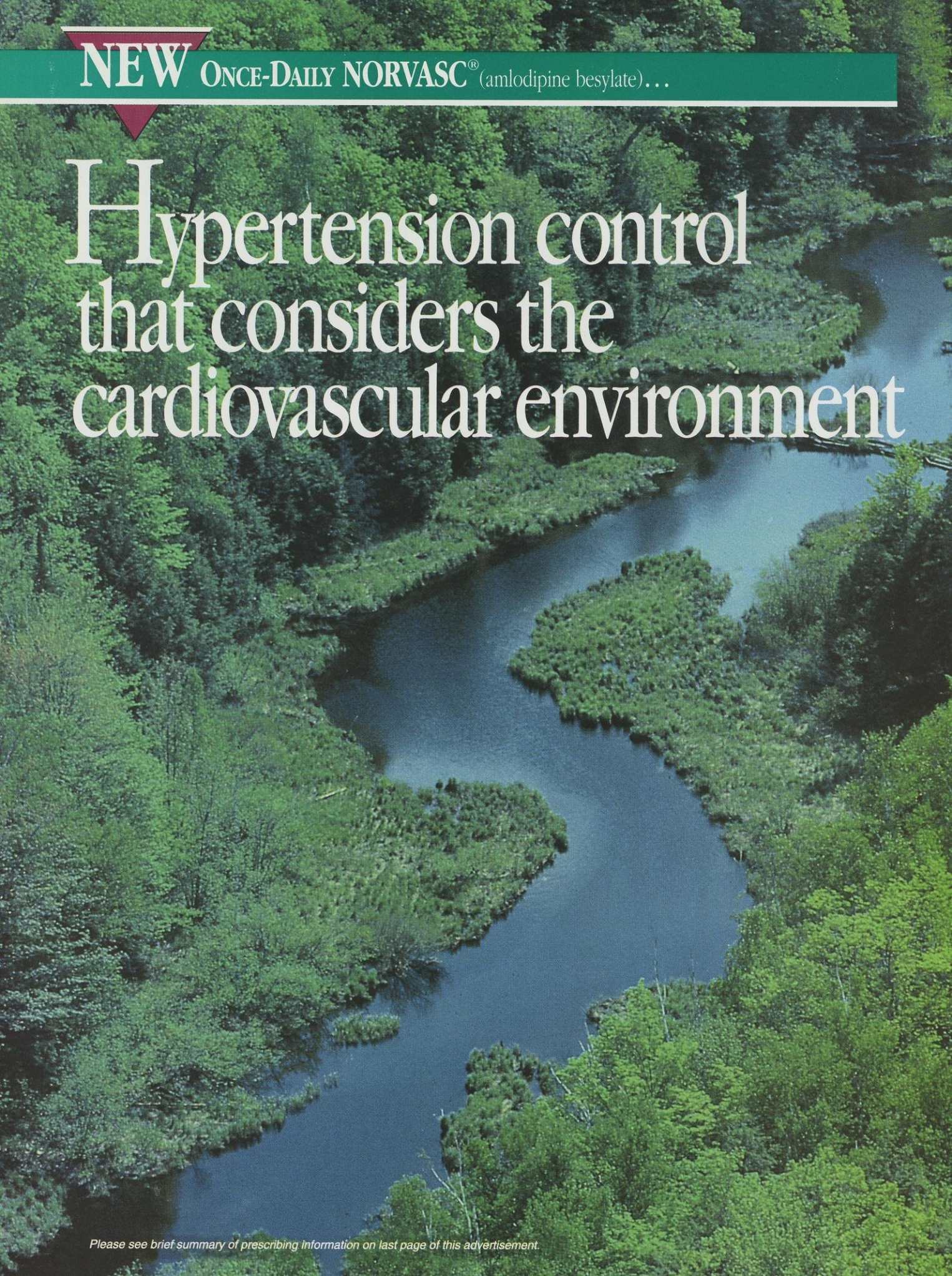
NORVASC®

(amlodipine besylate)

Confident 24-Hour Control That Considers the Cardiovascular Environment

NEW ONCE-DAILY NORVASC® (amlodipine besylate)...

Hypertension control that considers the cardiovascular environment



Please see brief summary of prescribing information on last page of this advertisement.

Arteriogram of peripheral vasculature

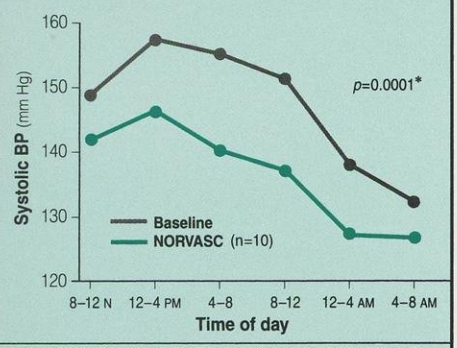
New NORVASC Acts Directly on Vascular Smooth Muscle, Reducing Blood Pressure Without Disturbing Heart Rate

EFFICACY

New, once-daily NORVASC provides effective yet gentle 24-hour control of hypertension with a gradual onset of action[1]

- Effective for mild, moderate, and severe hypertension[1]
- Effective in white, black, young, or old patients
- Over 80% of patients responding to NORVASC are controlled on 5 mg[1]

Mean systolic blood pressure (BP) over 24 hours (week 4 data)[1]



Results of a double-blind, randomized, parallel, placebo-controlled study of NORVASC on ambulatory BP in 15 evaluable hypertensive patients (diastolic BP range: 95 to 114 mm Hg): 10 on NORVASC, 5 on placebo. A 4-week, single-blind, placebo run-in period was followed by 4 weeks of double-blind therapy. Ambulatory BP was measured for 24 hours at the end of the placebo run-in phase and after double-blind therapy. (Data on file.[1])

*Average of mean BP values over 24 hours at week 4 versus baseline averages.

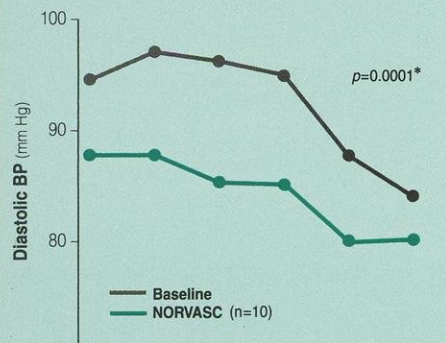
SAFETY

Excellent tolerability

- 92% of patients remained on NORVASC for 1 year in a long-term study[2]
- No clinically significant effects on heart rate[1] or cardiac conduction[1]; no negative inotropic effects at clinical doses in hemodynamic studies,† even when administered with beta blockers to humans[1]
- No adverse effect on lipid levels[1]
- No adjustment in the starting dose is required for patients with renal dysfunction, even those on hemodialysis[3]

†Similar hemodynamic findings, however, have been observed with agents possessing significant negative inotropic effects.

Mean diastolic BP over 24 hours (week 4 data)[1]



(Data on file.[1])

*Average of mean BP values over 24 hours at week 4 versus baseline averages.

NEW, ONCE-DAILY 5-mg and 10-mg tablets

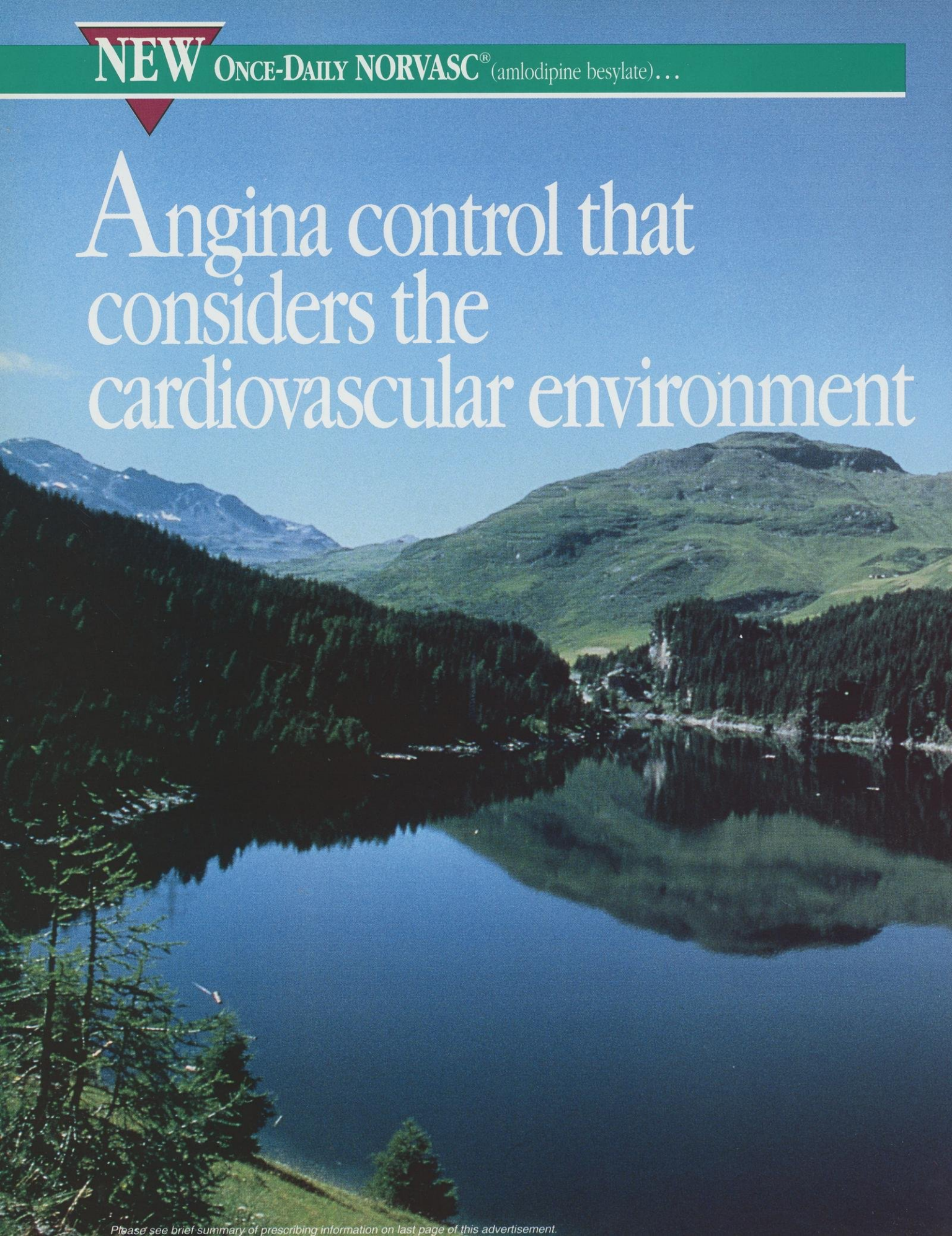
NORVASC®

(amlodipine besylate)

CONFIDENT 24-HOUR CONTROL THAT CONSIDERS THE CARDIOVASCULAR ENVIRONMENT

NEW ONCE-DAILY NORVASC® (amlodipine besylate)...

Angina control that considers the cardiovascular environment



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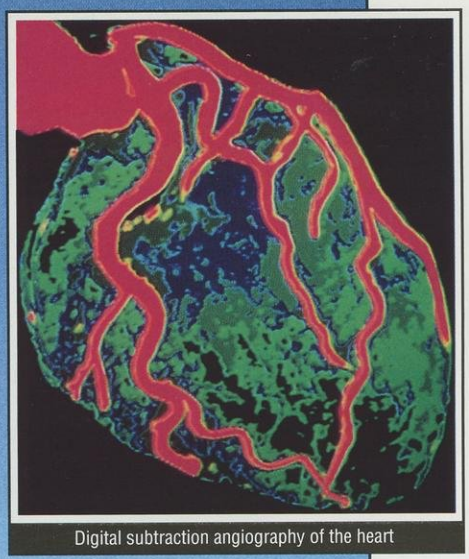


Digital subtraction angiography of the heart

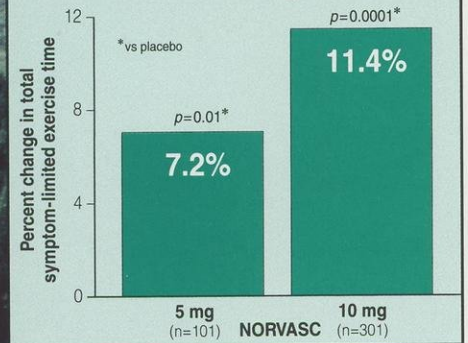
NEW NORVASC IS A VASODILATOR THAT REDUCES THE TOTAL PERIPHERAL RESISTANCE AGAINST WHICH THE HEART WORKS

EFFICACY

New, once-daily NORVASC provides 24-hour angina protection, including the morning hours[1]

- Effective for stable exertional angina
- Effective for vasospastic angina
- Effective alone or in combination with beta blockers

Change in symptom-limited exercise time measured 24 hours postdose[1]



Data from eight placebo-controlled, double-blind, randomized studies of the effect of NORVASC on symptom-limited exercise time. All studies included a 2-week, single-blind, placebo run-in period. The eight studies included five monotherapy trials and three add-on therapy trials. Treatment ranged from 4 to 6 weeks. Placebo group (n=297) had a 2.1% increase in symptom-limited exercise time. Exercise time at baseline: placebo, 480 sec; 5 mg, 523 sec; 10 mg, 493 sec. (Data on file.[1])

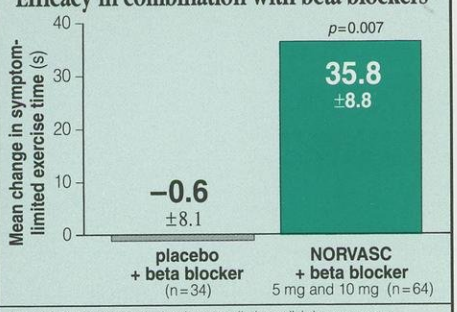
SAFETY

Well tolerated—minimal adverse effects

- No clinically significant effect on heart rate[1] or cardiac conduction[1]
- No negative inotropic effects at clinical doses in hemodynamic studies,‡ even when administered with beta blockers to humans[1]
- No drug interaction with digoxin, warfarin, or cimetidine[1]

‡ Similar hemodynamic findings, however, have been observed with agents possessing significant negative inotropic effects.

Efficacy in combination with beta blockers†[1]



Results of a double-blind, placebo-controlled, parallel-dose response, multicenter trial in 134 stable exertional angina patients. Patients received beta-blocker therapy for at least 4 weeks prior to entry. After a 2-week, single-blind, placebo run-in period with uninterrupted beta-blocker treatment, patients were randomized to receive NORVASC (2.5, 5, or 10 mg qd) or placebo for a 4-week treatment period. Data are presented for combined NORVASC groups (5 and 10 mg only) (n=67 patients entered) and placebo (n=34). Baseline values (NORVASC vs placebo)—symptom-limited exercise time (seconds): 518 (n=64) vs 498; angina onset: 400 (n=61) vs 368; time to 1-mm ST-segment depression: 457 (n=29) vs 440 (n=15). (Data on file.[1])

† Caution should be used in patients with heart failure who are receiving known cardiodepressants such as beta blockers in combination with NORVASC.

NEW, ONCE-DAILY

5-mg and 10-mg tablets

NORVASC®

(amlodipine besylate)

CONFIDENT 24-HOUR CONTROL THAT CONSIDERS THE CARDIOVASCULAR ENVIRONMENT

NEW ONCE-DAILY NORVASC® (amlodipine besylate)...

HYPERTENSION OR ANGINA CONTROL THAT CONSIDERS THE CARDIOVASCULAR ENVIRONMENT

SAFETY

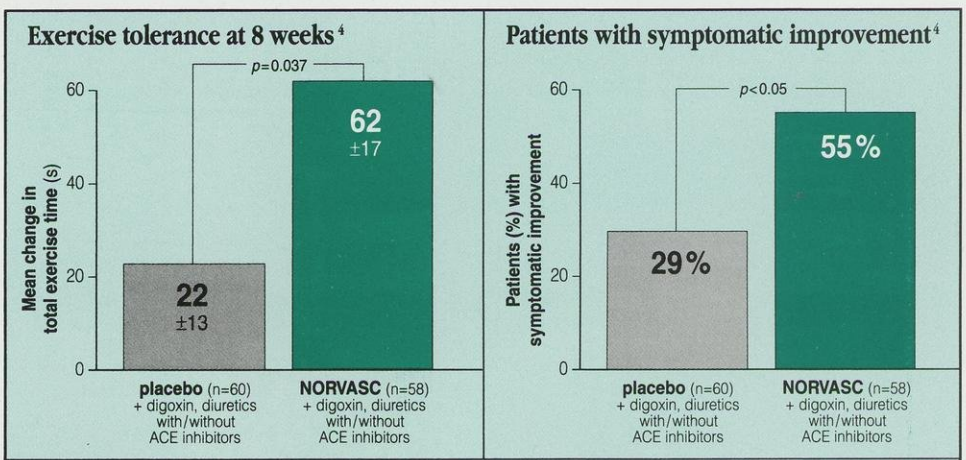
Well tolerated: only 1.5% of patients in placebo-controlled trials (n=1730) discontinued NORVASC due to adverse effects[1]

Dose-related side effects

Adverse event	NORVASC (%) 5 mg (n=296)	NORVASC (%) 10 mg (n=268)	placebo (%) (n=520)
Edema	3.0	10.8	0.6
Dizziness	3.4	3.4	1.5
Flushing	1.4	2.6	0.0
Palpitation	1.4	4.5	0.6

Caution should be exercised when using CCBs in any patient with heart failure

— In a double-blind study of 118 patients with mild to moderate CHF, NORVASC did not adversely affect cardiac function in patients with impaired LV function (LV ejection fraction <40%)[4]



Results of a randomized, multicenter, double-blind, placebo-controlled trial of NORVASC in 118 patients with well-compensated CHF. All had New York Heart Association (NYHA) Class II or III symptoms, with LV ejection fractions <40% (averaging 25%[1]). NORVASC dose: 10 mg qd. Patients were already on therapy with digoxin and diuretics, and 80 patients were also taking angiotensin-converting enzyme (ACE) inhibitors. (Adapted from Packer M et al, *J Am Coll Cardiol*, 1991.[4]) CHF patients did not have active angina or hypertension at the time of the study. Baseline exercise values: NORVASC, 570 sec; placebo, 613 sec. Symptomatology rating based on investigators' subjective global assessment. (Data on file.[1])

— In this study, NORVASC did not increase plasma norepinephrine levels and ejection fraction did not change[4]

— Studies in patients with NYHA Class IV heart failure have not been performed

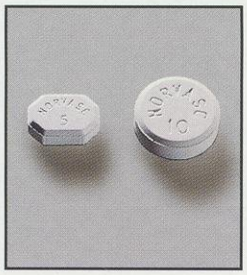
— NORVASC therapy, despite these findings, should be used with caution in patients with heart failure until safety in these patients can be confirmed with additional clinical experience

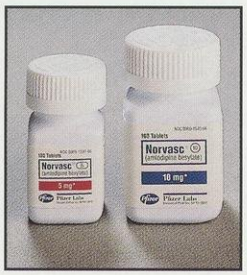
Please see brief summary of prescribing information on last page of this advertisement.

DOSING

Intrinsic once-daily dosing

- The usual starting dose is 5 mg in angina or hypertension
  - —In hypertension, small, fragile, or elderly individuals or patients with hepatic insufficiency may be started on 2.5 mg once daily
- Titration can proceed to 10 mg
  - —Most angina patients will require 10 mg
- Can be taken with or without food





Rx
Norvasc
5 mg
Sig: 1 tab
#30

NEW, ONCE-DAILY

5-mg and 10-mg tablets

NORVASC®

(amlodipine besylate)

CONFIDENT 24-HOUR CONTROL THAT CONSIDERS THE CARDIOVASCULAR ENVIRONMENT

References: **1.** Data on file. Pfizer Inc, New York, NY. **2.** The Treatment of Mild Hypertension Research Group. The treatment of mild hypertension study: a randomized, placebo-controlled trial of a nutritional-hygienic regimen along with various drug monotherapies. *Arch Intern Med.* 1991;151:1413-1423. **3.** Doyle GD, Donohue J, Carmody M, Laher M, Greb H, Volz M. Pharmacokinetics of amlodipine in renal impairment. *Eur J Clin Pharmacol.* 1989;36:205-208. **4.** Packer M, Nicod P, Khandheria BR, et al. Randomized, multicenter, double-blind, placebo-controlled evaluation of amlodipine in patients with mild-to-moderate heart failure. *J Am Coll Cardiol.* 1991;17:274A. Abstract.

Brief Summary
NORVASC® (amlodipine besylate) Tablets
For Oral Use
CONTRAINDICATIONS: NORVASC is contraindicated in patients with known sensitivity to amlodipine.
WARNINGS: 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.
PRECAUTIONS: General: Since the vasodilation induced by NORVASC is gradual in onset, acute hypotension has rarely been reported after oral administration of NORVASC. Nonetheless, caution should be exercised when administering NORVASC as with any other peripheral vasodilator particularly in patients with severe aortic stenosis.
Use in Patients with Congestive Heart Failure: Although hemodynamic studies and a controlled trial in NYHA Class II-III heart failure patients have shown that NORVASC did not lead to clinical deterioration as measured by exercise tolerance, left ventricular ejection fraction, and clinical symptomatology, studies have not been performed in patients with NYHA Class IV heart failure. In general, all calcium channel blockers should be used with caution in patients with heart failure.
Beta-Blocker Withdrawal: NORVASC is not a beta-blocker and therefore gives no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be by gradual reduction of the dose of the beta-blocker.
Patients with Hepatic Failure: Since NORVASC is extensively metabolized by the liver and the plasma elimination half-life (t ½) is 56 hours in patients with impaired hepatic function, caution should be exercised when administering NORVASC to patients with severe hepatic impairment.
Drug Interactions: *In vitro* data in human plasma indicate that NORVASC has no effect on the protein binding of drugs tested (digoxin, phenytoin, warfarin, and indomethacin). Special studies have indicated that the co-administration of NORVASC with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers; that co-administration with cimetidine did not alter the pharmacokinetics of amlodipine; and that co-administration with warfarin did not change the warfarin prothrombin response time.

In clinical trials, NORVASC has been safely administered with thiazide diuretics, beta-blockers, angiotensin converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.
Drug/Laboratory Test Interactions: None known.
Carcinogenesis, Mutagenesis, Impairment of Fertility: Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m^2 basis), was close to the maximum tolerated dose for mice but not for rats.

Mutagenicity studies revealed no drug related effects at either the gene or chromosome levels.

There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg on a mg/m^2 basis).
Pregnancy Category C: No evidence of teratogenicity or other embryo/fetal toxicity was found when pregnant rats or rabbits were treated orally with up to 10 mg/kg amlodipine (respectively 8 times* and 23 times* the maximum recommended human dose of 10 mg on a mg/m^2 basis) during their respective periods of major organogenesis. However, litter size was significantly decreased (by about 50%) and the number of intrauterine deaths was significantly increased (about 5-fold) in rats administered 10 mg/kg amlodipine for 14 days before mating and throughout mating and gestation. Amlodipine has been shown to prolong both the gestation period and the duration of labor in rats at this dose. There are no adequate and well-controlled studies in pregnant women. Amlodipine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Nursing Mothers: It is not known whether amlodipine is excreted in human milk. In the absence of this information, it is recommended that nursing be discontinued while NORVASC is administered.
Pediatric Use: Safety and effectiveness of NORVASC in children have not been established.
ADVERSE REACTIONS: NORVASC has been evaluated for safety in more than 11,000 patients in U.S. and foreign clinical trials. In general, treatment with NORVASC was well-tolerated at doses up to 10 mg daily. Most adverse reactions reported during therapy with NORVASC were of mild or moderate severity. In controlled clinical trials directly comparing NORVASC (N=1730) in doses up to 10 mg to placebo (N=1250), discontinuation of NORVASC due to adverse reactions was required in only about 1.5% of patients and was not significantly different from placebo (about 1%). The most common side effects are headache and edema. The incidence (%) of side effects which occurred in a dose related manner are as follows: edema (1.8% at 2.5 mg, 3.0% at 5.0 mg, and 10.8% at 10.0 mg, compared with 0.6% placebo); dizziness (1.1% at 2.5 mg, 3.4% at 5.0 mg, and 3.4% at 10.0 mg, compared with 1.5% placebo); flushing (0.7% at 2.5 mg, 1.4% at 5.0 mg, and 2.6% at 10.0 mg, compared with 0.0% placebo); and palpitation (0.7% at 2.5 mg, 1.4% at 5.0 mg, and 4.5% at 10.0 mg, compared with 0.6% placebo).

Other adverse experiences which were not clearly dose related but which were reported with an incidence greater than 1.0% in placebo-controlled clinical trials include the following: headache (7.3%, compared with 7.8% placebo); fatigue (4.5%, compared with 2.8% placebo); nausea (2.9%, compared with 1.9% placebo); abdominal pain (1.6%, compared with 0.3% placebo); and somnolence (1.4%, compared with 0.6% placebo).

For several adverse experiences that appear to be drug and dose related, there was a greater incidence in women than men associated with amlodipine treatment as follows: edema (5.6% in men, 14.6% in women, compared with a placebo incidence in men of 1.4% and 5.1% in women); flushing (1.5% in men, 4.5% in women, compared with a placebo incidence of 0.3% in men and 0.9% in women); palpitations (1.4% in men, 3.3% in women, compared with a placebo incidence of 0.9% in men and 0.9% in women); and somnolence (1.3% in men, 1.6% in women, compared with a placebo incidence of 0.8% in men and 0.3% in women).

The following events occurred in ≤1% but >0.1% of patients in controlled clinical trials or under conditions of open trials or marketing experience where a causal relationship is uncertain; they are listed to alert the physician to a possible relationship: **cardiovascular:** arrhythmia, bradycardia, chest pain, hypotensidn, peripheral ischemia, syncope, tachycardia, postural dizziness, postural hypotension; **central and peripheral nervous system:** hypoesthesia, paresthesia, tremor, vertigo; **gastrointestinal:** anorexia, constipation, dyspepsia,** dysphagia, diarrhea, flatulence, vomiting; **general:** asthenia,** back pain, hot flushes, malaise, pain, rigors, weight gain; **musculo-skeletal system:** arthralgia, arthrosis, muscle cramps,** myalgia; **psychiatric:** sexual dysfunction (male** and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization; **respiratory system:** dyspnea,** epistaxis; **skin and appendages:** pruritus,** rash,** rash erythematous, rash maculopapular; **special senses:** abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus; **urinary system:** micturition frequency, micturition disorder, nocturia; **autonomic nervous system:** dry mouth, sweating increased; **metabolic and nutritional:** thirst; **hemopoietic:** purpura.

The following events occurred in ≤0.1% of patients: cardiac failure, pulse irregularity, extrasystoles, skin discoloration, urticaria, skin dryness, alopecia, dermatitis, muscle weakness, twitching, ataxia, hypertonia, migraine, cold and clammy skin, apathy, agitation, amnesia, gastritis, increased appetite, loose stools, coughing, rhinitis, dysuria, polyuria, parosmia, taste perversion, abnormal visual accommodation, and xerophthalmia.

Other reactions occurred sporadically in single patients and cannot be distinguished from concurrent disease states or medications.

NORVASC therapy has not been associated with clinically significant changes in routine laboratory tests. No clinically relevant changes were noted in serum potassium, serum glucose, total triglycerides, total cholesterol, HDL cholesterol, uric acid, blood urea nitrogen, creatinine or liver function tests.

NORVASC has been used safely in patients with chronic obstructive pulmonary disease, well compensated congestive heart failure, peripheral vascular disease, diabetes mellitus, and abnormal lipid profiles.
OVERDOSAGE: Single oral doses of 40 mg/kg and 100 mg/kg in mice and rats, respectively, caused deaths. A single oral dose of 4 mg/kg or higher in dogs caused a marked peripheral vasodilation and hypotension.

Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia. In humans, experience with intentional overdosage of NORVASC is limited. Reports of intentional overdosage include a patient who ingested 250 mg and was asymptomatic and was not hospitalized; another (120 mg) was hospitalized, underwent gastric lavage and remained normotensive; the third (105 mg) was hospitalized and had hypotension (90/50 mmHg) which normalized following plasma expansion. A patient who took 70 mg amlodipine and an unknown quantity of benzodiazepine in a suicide attempt, developed shock which was refractory to treatment and died the following day with abnormally high benzodiazepine plasma concentration. A case of accidental drug overdose has been documented in a 19 month old male who ingested 30 mg amlodipine (about 2 mg/kg). During the emergency room presentation, vital signs were stable with no evidence of hypotension, but a heart rate of 180 bpm. Ipecac was administered 3.5 hours after ingestion and on subsequent observation (overnight) no sequelae were noted.

If massive overdose should occur, active cardiac and respiratory monitoring should be instituted. Frequent blood pressure measurements are essential. Should hypotension occur, cardiovascular support including elevation of the extremities and the judicious administration of fluids should be initiated. If hypotension remains unresponsive to these conservative measures, administration of vasopressors (such as phenylephrine), should be considered with attention to circulating volume and urine output. Intravenous calcium gluconate may help to reverse the effects of calcium entry blockade. As NORVASC is highly protein bound, hemodialysis is not likely to be of benefit.

* Based on patient weight of 50 kg.
**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.

More detailed professional information available on request.
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Pfizer Labs