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Printed on recycled paper

ISBN: 1-56363-330-2

Navane IM—Cont.

ADVERSE REACTIONS

NOTE: Not all of the following adverse reactions have been reported with Navane. However, since Navane has certain chemical and pharmacologic similarities to the phenothiazines, all of the known side effects and toxicity associated with phenothiazine therapy should be borne in mind when Navane is used.

Cardiovascular Effects: Tachycardia, hypotension, lightheadedness, and syncope. In the event hypotension occurs, epinephrine should not be used as a pressor agent since a paradoxical further lowering of blood pressure may result. Nonspecific EKG changes have been observed in some patients receiving Navane. These changes are usually reversible and frequently disappear on continued Navane therapy. The clinical significance of these changes is not known.

CNS Effects: Drowsiness, usually mild, may occur although it usually subsides with continuation of Navane therapy. The incidence of sedation appears similar to that of the piperazine group of phenothiazines, but less than that of certain aliphatic phenothiazines. Restlessness, agitation and insomnia have been noted with Navane. Seizures and paradoxical exacerbation of psychotic symptoms have occurred with Navane infrequently.

Hyperreflexia has been reported in infants delivered from mothers having received structurally related drugs.

In addition, phenothiazine derivatives have been associated with cerebral edema and cerebrospinal fluid abnormalities.

Extrapyramidal symptoms, such as pseudo-parkinsonism, akathisia, and dystonia have been reported. Management of these extrapyramidal symptoms depends upon the type and severity. Rapid relief of acute symptoms may require the use of an injectable antiparkinson agent. More slowly emerging symptoms may be managed by reducing the dosage of Navane and/or administering an oral antiparkinson agent.

Persistent Tardive Dyskinesia: As with all antipsychotic agents tardive dyskinesia may appear in some patients on long term therapy or may occur after drug therapy has been discontinued. The syndrome is characterized by rhythmical involuntary movements of the tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities.

Since early detection of tardive dyskinesia is important, patients should be monitored on an ongoing basis. It has been reported that fine vermicular movement of the tongue may be an early sign of the syndrome. If this or any other presentation of the syndrome is observed, the clinician should consider possible discontinuation of neuroleptic medication. (See WARNINGS section.)

Hepatic Effects: Elevations of serum transaminase and alkaline phosphatase, usually transient, have been infrequently observed in some patients. No clinically confirmed cases of jaundice attributable to Navane (thiothixene hydrochloride) have been reported.

Hematologic Effects: As is true with certain other psychotropic drugs, leukopenia and leucocytosis, which are usually transient, can occur occasionally with Navane. Other antipsychotic drugs have been associated with agranulocytosis, eosinophilia, hemolytic anemia, thrombocytopenia and pancytopenia.

Allergic Reactions: Rash, pruritus, urticaria, and rare cases of anaphylaxis have been reported with Navane. Undue exposure to sunlight should be avoided. Although not experienced with Navane, exfoliative dermatitis, contact dermatitis (in nursing personnel), have been reported with certain phenothiazines.

Endocrine Disorders: Lactation, moderate breast enlargement and amenorrhea have occurred in a small percentage of females receiving Navane. If persistent, this may necessitate a reduction in dosage or the discontinuation of therapy. Phenothiazines have been associated with false positive pregnancy tests, gynecomastia, hypoglycemia, hyperglycemia, and glycosuria.

Autonomic Effects: Dry mouth, blurred vision, nasal congestion, constipation, increased sweating, increased salivation, and impotence have occurred infrequently with Navane therapy. Phenothiazines have been associated with miosis, mydriasis, and adynamic ileus.

Other Adverse Reactions: Hyperpyrexia, anorexia, nausea, vomiting, diarrhea, increase in appetite and weight, weakness or fatigue, polydipsia and peripheral edema.

Although not reported with Navane, evidence indicates there is a relationship between phenothiazine therapy and the occurrence of a systemic lupus erythematosus-like syndrome.

Neuroleptic Malignant Syndrome (NMS): Please refer to the text regarding NMS in the WARNINGS section.

NOTE: Sudden deaths have occasionally been reported in patients who have received certain phenothiazine derivatives. In some cases the cause of death was apparently cardiac arrest or asphyxia due to failure of the cough reflex. In others, the cause could not be determined nor could it be established that death was due to phenothiazine administration.

DOSAGE AND ADMINISTRATION

Preparation

Navane (thiothixene hydrochloride) Intramuscular For Injection must be reconstituted with 2.2 ml of sterile water for injection.

For Intramuscular Use Only

Dosage of Navane should be individually adjusted depending on the chronicity and severity of the condition. In general, small doses should be used initially and gradually increased to the optimal effective level, based on patient response.

Usage in children under 12 years of age is not recommended.

Where more rapid control and treatment of acute behavior is desirable, the intramuscular form of Navane may be indicated. It is also of benefit where the very nature of the patient's symptomatology, whether acute or chronic, renders oral administration impractical or even impossible.

For treatment of acute symptomatology or in patients unable or unwilling to take oral medication, the usual dose is 4 mg of Navane Intramuscular For Injection administered 2 to 4 times daily. Dosage may be increased or decreased depending on response. Most patients are controlled on a total daily dosage of 16 to 20 mg. The maximum recommended dosage is 30 mg/day. An oral form should supplant the injectable form as soon as possible. It may be necessary to adjust the dosage when changing from the intramuscular to oral dosage forms. Dosage recommendations for Navane Capsules and Concentrate can be found in the Navane oral package insert.

OVERDOSAGE

Manifestations include muscular twitching, drowsiness, and dizziness. Symptoms of gross overdosage may include CNS depression, rigidity, weakness, torticollis, tremor, salivation, dysphagia, hypotension, disturbances of gait, or coma.

Treatment: Essentially symptomatic and supportive. Keep patient under careful observation and maintain an open airway, since involvement of the extrapyramidal system may produce dysphagia and respiratory difficulty in severe overdosage. If hypotension occurs, the standard measures for managing circulatory shock should be used (I.V. fluids and/or vasoconstrictors).

If a vasoconstrictor is needed, levarterenol and phenylephrine are the most suitable drugs. Other pressor agents, including epinephrine, are not recommended, since phenothiazine derivatives may reverse the usual pressor elevating action of these agents and cause further lowering of blood pressure.

If CNS depression is marked, symptomatic treatment is indicated. Extrapyramidal symptoms may be treated with antiparkinson drugs.

There are no data on the use of peritoneal or hemodialysis, but they are known to be of little value in phenothiazine intoxication.

HOW SUPPLIED

Navane (thiothixene hydrochloride) Intramuscular For Injection is available in amber glass vials in packages of 10 vials (NDC 0049-5765-83). When reconstituted with 2.2 ml of STERILE WATER FOR INJECTION, each ml contains thiothixene hydrochloride equivalent to 5 mg of thiothixene, and 59.6 mg of mannitol. The reconstituted solution of Navane Intramuscular For Injection may be stored for 48 hours at room temperature before discarding.

70-4177-00-4

Revised January 1988

NORVASC® ℞

[nor 'vask]

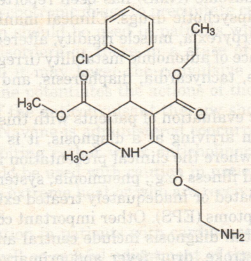
(amlodipine besylate)

Tablets

DESCRIPTION

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

NORVASC is chemically described as (R.S.) 3-ethyl-5-methyl-2-(2-amino-ethoxymethyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate benzenesulphonate. Its empirical formula is $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$, and its structural formula is:



$C_6H_6O_3S$

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. NORVASC (amlodipine besylate) tablets are formulated as white tablets equivalent to 2.5, 5 and 10 mg of amlodipine for oral administration. In addition to the active ingredient, amlodipine besylate, each tablet contains the following inactive ingredients: microcrystalline cellulose, dibasic calcium phosphate anhydrous, sodium starch glycolate, and magnesium stearate.

CLINICAL PHARMACOLOGY

Mechanism of Action: NORVASC 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 NORVASC 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. NORVASC 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 NORVASC. Within the physiologic pH range, NORVASC 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.

NORVASC 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 NORVASC relieves angina have not been fully delineated, but are thought to include the following:

Exertional Angina: In patients with exertional angina, NORVASC 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: NORVASC has been demonstrated to block constriction and restore blood flow in coronary arteries and arterioles in response to calcium, potassium epinephrine, serotonin, and thromboxane A_2 analog in experimental animal models and in human coronary vessels *in vitro*. This inhibition of coronary spasm is responsible for the effectiveness of NORVASC in vasospastic (Prinzmetal's or variant) angina.

Pharmacokinetics and Metabolism: After oral administration of therapeutic doses of NORVASC, absorption produces peak plasma concentrations between 6 and 12 hours. Absolute bioavailability has been estimated to be between 64 and 90%. The bioavailability of NORVASC is not altered by the presence of food.

NORVASC is extensively (about 90%) converted to inactive metabolites via hepatic metabolism with 10% of the parent compound and 60% of the metabolites excreted in the urine. *Ex vivo* studies have shown that approximately 93% of the circulating drug is bound to plasma proteins in hypertensive patients. Elimination from the plasma is biphasic with a terminal elimination half-life of about 30–50 hours. Steady-state plasma levels of NORVASC are reached after 7 to 8 days of consecutive daily dosing.

The pharmacokinetics of NORVASC are not significantly influenced by renal impairment. Patients with renal failure may therefore receive the usual initial dose.

Elderly patients and patients with hepatic insufficiency have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40–60%, and a lower initial dose may be required. A similar increase in AUC was observed in patients with moderate to severe heart failure.

Pharmacodynamics: *Hemodynamics* Following administration of therapeutic doses to patients with hypertension, NORVASC 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 administration of oral 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 NORVASC 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 NORVASC 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 NORVASC 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, NORVASC 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 normals or well-compensated patients with heart failure with agents possessing significant negative inotropic effects.

Studies in Patients with Congestive Heart Failure: NORVASC 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 LVEF. In a long-term (follow-up at least 6 months, mean 13.8 months) placebo-controlled mortality/morbidity study of NORVASC 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, NORVASC 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 NORVASC and 246/583 (42%) for patients on placebo; the cardiac morbid events represented about 25% of the endpoints in the study.

Electrophysiologic Effects: NORVASC 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 NORVASC and concomitant beta blockers. In clinical studies in which NORVASC 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, NORVASC therapy did not alter electrocardiographic intervals or produce higher degrees of AV blocks.

Effects in Hypertension: The antihypertensive efficacy of NORVASC has been demonstrated in a total of 15 double-blind, placebo-controlled, randomized studies involving 800 patients on NORVASC 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.

Effects in Chronic Stable Angina: The effectiveness of 5–10 mg/day of NORVASC 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 NORVASC, 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 NORVASC 10 mg, and averaged 7.9% (38 sec) for NORVASC 5 mg. NORVASC 10 mg also increased time to 1 mm ST segment deviation in several studies and decreased angina attack rate. The sustained efficacy of NORVASC 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).

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

INDICATIONS AND USAGE

1. Hypertension

NORVASC is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

2. Chronic Stable Angina

NORVASC is indicated for the treatment of chronic stable angina. NORVASC may be used alone or in combination with other antianginal agents.

3. Vasospastic Angina (Prinzmetal's or Variant Angina)

NORVASC is indicated for the treatment of confirmed or suspected vasospastic angina. NORVASC may be used as monotherapy or in combination with other antianginal drugs.

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: In general, calcium channel blockers should be used with caution in patients with heart failure. NORVASC (5–10 mg per day) has been studied in a placebo-controlled trial of 1153 patients with NYHA Class III or IV heart failure (see CLINICAL PHARMACOLOGY) on stable doses of ACE inhibitor, digoxin, and diuretics. Follow-up was at least 6 months, with a mean of about 14 months. There was no overall adverse effect on survival or cardiac morbidity (as defined by life-threatening arrhythmia, acute myocardial infarction, or hospitalization for worsened heart failure). NORVASC 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 LVEF.

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 beta-blocker.

Patients with Hepatic Failure: Since NORVASC is extensively metabolized by the liver and the plasma elimination half-life (t 1/2) 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.

*Based on patient weight of 50 kg.

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:

Adverse Event	2.5 mg N=275	5.0 mg N=296	10.0 mg N=268	Placebo 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 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:

Placebo-Controlled Studies

	NORVASC (%) (N=1730)	PLACEBO (%) (N=1250)
Headache	7.3	7.8
Fatigue	4.5	2.8
Nausea	2.9	1.9
Abdominal Pain	1.6	0.3
Somnolence	1.4	0.6

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 shown in the following table:

ADR	NORVASC M=% (N=1218)	NORVASC F=% (N=512)	PLACEBO M=% (N=914)	PLACEBO F=% (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

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 (including ventricular tachycardia and atrial fibrillation), 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, gingival hyperplasia.

General: asthenia,** back pain, hot flushes, malaise, pain, rigors, weight gain.

Musculoskeletal 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.

**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.

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 and cannot be distinguished from medications or concurrent disease states such as myocardial infarction and angina.

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, or creatinine.

The following postmarketing event has been reported infrequently where a causal relationship is uncertain: gynecomastia. In postmarketing experience, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis) in some cases severe enough to require hospitalization have been reported in association with use of amlodipine.

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 over-

Continued on next page

Norvasc—Cont.

dosage 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 2mg/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.

DOSAGE AND ADMINISTRATION

The usual initial antihypertensive oral dose of NORVASC is 5 mg once daily with a maximum dose of 10 mg once daily. Small, fragile, or elderly individuals, or patients with hepatic insufficiency may be started on 2.5 mg once daily and this dose may be used when adding NORVASC to other antihypertensive therapy.

Dosage should be adjusted according to each patient's need. In general, titration should proceed over 7 to 14 days so that the physician can fully assess the patient's response to each dose level. Titration may proceed more rapidly, however, if clinically warranted, provided the patient is assessed frequently.

The recommended dose for chronic stable or vasospastic angina is 5–10 mg, with the lower dose suggested in the elderly and in patients with hepatic insufficiency. Most patients will require 10 mg for adequate effect. See ADVERSE REACTIONS section for information related to dosage and side effects.

Co-administration with Other Antihypertensive and/or Antianginal Drugs: NORVASC has been safely administered with thiazides, ACE inhibitors, betablockers, long-acting nitrates, and/or sublingual nitroglycerin.

HOW SUPPLIED

NORVASC®–2.5 mg Tablets (amlodipine besylate equivalent to 2.5 mg of amlodipine per tablet) are supplied as white, diamond, flat-faced, beveled edged engraved with "NORVASC" on one side and "2.5" on the other side and supplied as follows:

NDC 0069-1520-68	Bottle of 90
NDC 0069-1520-66	Bottle of 100

NORVASC®–5 mg Tablets (amlodipine besylate equivalent to 5 mg of amlodipine per tablet) are white, elongated octagon, flat-faced, beveled edged engraved with both "NORVASC" and "5" on one side and plain on the other side and supplied as follows:

NDC 0069-1530-68	Bottle of 90
NDC 0069-1530-66	Bottle of 100
NDC 0069-1530-41	Unit Dose package of 100
NDC 0069-1530-72	Bottle of 300

NORVASC®–10 mg Tablets (amlodipine besylate equivalent to 10 mg of amlodipine per tablet) are white, round, flat-faced, beveled edged engraved with both "NORVASC" and "10" on one side and plain on the other side and supplied as follows:

NDC 0069-1540-68	Bottle of 90
NDC 0069-1540-66	Bottle of 100
NDC 0069-1540-41	Unit Dose package of 100

Store bottles at controlled room temperature, 59° to 86°F (15° to 30°C) and dispense in tight, light-resistant containers (USP).

69-4782-00-6 Revised November 1996

Shown in Product Identification Guide, page 331

Buffered PFIZERPEN®
(penicillin G potassium) for Injection

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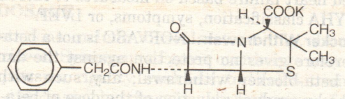
DESCRIPTION

Buffered Pfizerpen® (penicillin G potassium) for Injection is a sterile, pyrogen-free powder for reconstitution. Buffered Pfizerpen for Injection is an antibacterial agent for intramuscular, continuous intravenous drip, intrapleural or other local infusion, and intrathecal administration.

Each million units contains approximately 6.8 milligrams of sodium (0.3 mEq) and 65.6 milligrams of potassium (1.68 mEq).

Chemically, Pfizerpen is monopotassium 3,3-dimethyl-7-oxo-6-(2-phenylacetamido)-4-thia-1-azabicyclo (3.2.0) heptane-2-carboxylate. It has a molecular weight of 372.48 and the following chemical structure:



Formula
$C_{16}H_{17}KN_2O_4S$

Penicillin G potassium is a colorless or white crystal, or a white crystalline powder which is odorless, or practically so, and moderately hygroscopic. Penicillin G potassium is very soluble in water. The pH of the reconstituted product is between 6.0–8.5.

CLINICAL PHARMACOLOGY

Aqueous penicillin G is rapidly absorbed following both intramuscular and subcutaneous injection. Initial blood levels following parenteral administration are high but transient. Penicillins bind to serum proteins, mainly albumin. Therapeutic levels of the penicillins are easily achieved under normal circumstances in extracellular fluid and most other body tissues. Penicillins are distributed in varying degrees into pleural, pericardial, peritoneal, ascitic, synovial, and interstitial fluids. Penicillins are excreted in breast milk. Penetration into the cerebrospinal fluid, eyes, and prostate is poor. Penicillins are rapidly excreted in the urine by glomerular filtration and active tubular secretion, primarily as unchanged drug. Approximately 60 percent of the total dose of 300,000 units is excreted in the urine within this 5-hour period. For this reason, high and frequent doses are required to maintain the elevated serum levels desirable in treating certain severe infections in individuals with normal kidney function. In neonates and young infants, and in individuals with impaired kidney function, excretion is considerably delayed.

Microbiology

Penicillin G exerts a bactericidal action against penicillin-susceptible microorganisms during the stage of active multiplication. It acts through the inhibition of biosynthesis of cell wall mucopeptide rendering the cell wall osmotically unstable. It is not active against the penicillinase-producing bacteria, which include many strains of staphylococci. While *in vitro* studies have demonstrated that susceptibility of most strains of the following organisms, clinical efficacy for infections other than those included in the INDICATIONS AND USAGE section has not been documented. Penicillin G exerts high *in vitro* activity against staphylococci (except penicillinase-producing strains), streptococci (groups A, C, G, H, L, and M), and pneumococci. Other organisms susceptible to penicillin G are *N. gonorrhoeae, Corynebacterium diphtheriae, Bacillus anthracis,* Clostridia, *Actinomyces bovis, Streptobacillus moniliformis, Listeria monocytogenes* and Leptospira. *Treponema pallidum* is extremely sensitive to the bactericidal action of penicillin G. Some species of gram-negative bacilli are sensitive to moderate to high concentrations of the drug obtained with intravenous administration. These include most strains of *Escherichia coli;* all strains of *Proteus mirabilis,* Salmonella and Shigella; and some strains of *Aerobacter aerogenes* and *Alcaligenes faecalis.*

Penicillin acts synergistically with gentamicin or tobramycin against many strains of enterococci.

Susceptibility Testing: Penicillin G Susceptibility Powder or 10 units Penicillin G Susceptibility Discs may be used to determine microbial susceptibility to penicillin G using one of the following standard methods recommended by the National Committee for Laboratory Standards:

M2-A3, "Performance Standards for Antimicrobial Disk Susceptibility Tests"

M7-A, "Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically"

M11-A, "Reference Agar Dilution Procedure for Antimicrobial Susceptibility Testing of Anaerobic Bacteria"

M17-P, "Alternative Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria"

Tests should be interpreted by the following criteria:

[See tables above]

Interpretations of susceptible, intermediate, and resistant correlate zone size diameters with MIC values. A laboratory report of "susceptible" indicates that the suspected causative microorganism most likely will respond to therapy with penicillin G. A laboratory report of "resistant" indicates that the infecting microorganism most likely will not respond to therapy. A laboratory report of "moderately susceptible" indicates that the microorganism is most likely susceptible if a high dosage of penicillin G is used, or if the infection is such that high levels of penicillin G may be attained, as in urine. A report of "intermediate" using the disk diffusion method may be considered an equivocal result, and dilution tests may be indicated.

Control organisms are recommended for susceptibility testing. Each time the test is performed the following organisms should be included. The range for zones of inhibition is shown below:

Control Organism	Zone of Inhibition Range
Staphylococcus aureus (ATCC 25923)	27–35

Zone Diameter, nearest whole mm

	Susceptible	Moderately Susceptible	Resistant
Staphylococci	≥29	—	≤28
N. gonorrhoeae	≥20	—	≤19
Enterococci	—	≥15	≤14
Non-enterococcal streptococci and *L. monocytogenes*	≥28	20–27	≤19

Approximate MIC Correlates

	Susceptible	Resistant
Staphylococci	≤0.1 µg/mL	β-lactamase
N. gonorrhoeae	≤0.1 µg/mL	β-lactamase
Enterococci	—	≥16 µg/mL
Non-enterococcal streptococci and *L. monocytogenes*	≤0.12 µg/mL	≥ 4 µg/mL

INDICATIONS AND USAGE

Aqueous penicillin G (parenteral) is indicated in the therapy of severe infections caused by penicillin G-susceptible microorganisms when rapid and high penicillin levels are required in the conditions listed below. Therapy should be guided by bacteriological studies (including susceptibility tests) and by clinical response.

The following infections will usually respond to adequate dosage of penicillin G (parenteral):

Streptococcal infections.

NOTE: Streptococci in groups A, C, H, G, L, and M are very sensitive to penicillin G. Some group D organisms are sensitive to the high serum levels obtained with aqueous penicillin G.

Aqueous penicillin G (parenteral) is the penicillin dosage form of choice for bacteremia, empyema, severe pneumonia, pericarditis, endocarditis, meningitis, and other severe infections caused by sensitive strains of the gram-positive species listed above.

Pneumococcal infections.

Staphylococcal infections—penicillin G sensitive.

Other infections:

Anthrax.

Actinomycosis.

Clostridial infections (including tetanus).

Diphtheria (to prevent carrier state).

Erysipeloid *(Erysipelothrix insidiosa)* endocarditis.

Fusospirochetal infections—severe infections of the oropharynx (Vincent's), lower respiratory tract and genital area due to *Fusobacterium fusiformisans* spirochetes.

Gram-negative bacillary infections (bacteremias)–*(E. coli, A. aerogenes, A. faecalis,* Salmonella, Shigella and *P. mirabilis).*

Listeria infections *(Listeria monocytogenes).*

Meningitis and endocarditis.

Pasteurella infections *(Pasteurella multocida).*

Bacteremia and meningitis.

Rat-bite fever *(Spirillum minus* or *Streptobacillus moniliformis).*

Gonorrheal endocarditis and arthritis *(N. gonorrhoeae).*

Syphilis *(T. pallidum)* including congenital syphilis.

Meningococcic meningitis.

Although no controlled clinical efficacy studies have been conducted, aqueous crystalline penicillin G for injection and penicillin G procaine suspension have been suggested by the American Heart Association and the American Dental Association for use as part of a combined parenteral-oral regimen for prophylaxis against bacterial endocarditis in patients with congenital heart disease or rheumatic, or other acquired valvular heart disease when they undergo dental procedures and surgical procedures of the upper respiratory tract.[1] Since it may happen that *alpha* hemolytic streptococci relatively resistant to penicillin may be found when patients are receiving continuous oral penicillin for secondary prevention of rheumatic fever, prophylactic agents other than penicillin may be chosen for these patients and prescribed in addition to their continuous rheumatic fever prophylactic regimen.

NOTE: When selecting antibiotics for the prevention of bacterial endocarditis, the physician or dentist should read the full joint statement of the American Heart Association and the American Dental Association.[1]