

**HYPERTENIPINE - amlodipine besylate, arginine**  
**Physician Therapeutics LLC**

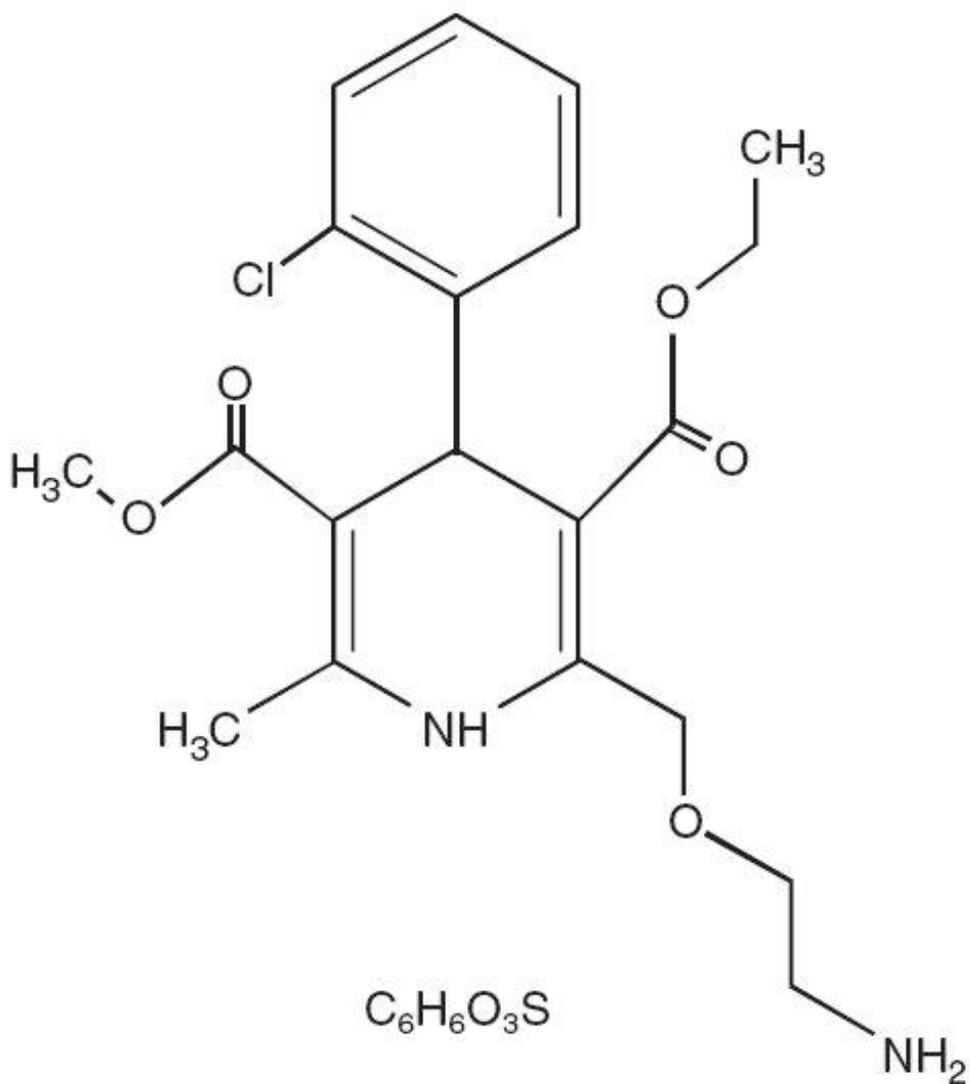
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**Hypertenipine-2.5**

**DESCRIPTION**

Amlodipine besylate, USP is a long-acting calcium channel blocker.

Amlodipine besylate, USP is chemically described as 3-Ethyl-5-methyl ( $\pm$ )-2-[(2-aminoethoxy) methyl] - 4 - (2 - c h l o r o p h e n y l) - 1 , 4 - d i h y d r o - 6 - m e t h y l - 3 , 5 - p y r i d i n e d i c a r b o x y l a t e , monobenzenesulphonate. Its molecular formula is  $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$ , and its structural formula is:



Amlodipine besylate, USP is a white crystalline powder with a molecular weight of 567.1. It is slightly soluble in water and sparingly soluble in ethanol. 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, USP, each tablet contains the following inactive ingredients: microcrystalline cellulose, dibasic calcium phosphate anhydrous, sodium starch glycolate, and magnesium stearate.

## CLINICAL PHARMACOLOGY

### Mechanism of Action

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

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

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

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

**Vasospastic Angina:** Amlodipine besylate 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<sub>2</sub> analog in experimental animal models and in human coronary vessels in vitro. This inhibition of coronary spasm is responsible for the effectiveness of amlodipine besylate in vasospastic (Prinzmetal's or variant) angina.

### Pharmacokinetics and Metabolism

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

Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism with 10% of the parent compound and 60% of the metabolites excreted in the urine. 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 amlodipine are reached after 7 to 8 days of consecutive daily dosing.

The pharmacokinetics of amlodipine 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.

## Pediatric Patients

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

## Pharmacodynamics

**Hemodynamics** Following administration of therapeutic doses to patients with hypertension, amlodipine besylate produces vasodilation resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing. Although the acute intravenous administration of amlodipine decreases arterial blood pressure and increases heart rate in hemodynamic studies of patients with chronic stable angina, chronic oral administration of amlodipine in clinical trials did not lead to clinically significant changes in heart rate or blood pressures in normotensive patients with angina.

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

In hypertensive patients with normal renal function, therapeutic doses of amlodipine besylate resulted in a decrease in renal vascular resistance and an increase in glomerular filtration rate and effective renal plasma flow without change in filtration fraction or proteinuria.

As with other calcium channel blockers, hemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with amlodipine besylate have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume. In hemodynamic studies, amlodipine besylate 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.

**Electrophysiologic Effects:** Amlodipine besylate does not change sinoatrial nodal function or atrioventricular conduction in intact animals or man. In patients with chronic stable angina, intravenous administration of 10 mg did not significantly alter A-H and H-V conduction and sinus node recovery time after pacing. Similar results were obtained in patients receiving amlodipine besylate and concomitant beta blockers. In clinical studies in which amlodipine besylate was administered in combination with beta-blockers to patients with either hypertension or angina, no adverse effects on electrocardiographic parameters were observed. In clinical trials with angina patients alone, amlodipine besylate therapy did not alter electrocardiographic intervals or produce higher degrees of AV blocks.

## Clinical Studies

### Effects in Hypertension

**Adult Patients:** The antihypertensive efficacy of amlodipine besylate has been demonstrated in a total of 15 double-blind, placebo-controlled, randomized studies involving 800 patients on amlodipine

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

**Pediatric Patients:** Two-hundred sixty-eight hypertensive patients aged 6 to 17 years were randomized first to amlodipine besylate 2.5 or 5 mg once daily for 4 weeks and then randomized again to the same dose or to placebo for another 4 weeks. Patients receiving 5 mg at the end of 8 weeks had lower blood pressure than those secondarily randomized to placebo. The magnitude of the treatment effect is difficult to interpret, but it is probably less than 5 mmHg systolic on the 5 mg dose. Adverse events were similar to those seen in adults.

#### Effects in Chronic Stable Angina:

The effectiveness of 5 to 10 mg/day of amlodipine besylate in exercise-induced angina has been evaluated in 8 placebo-controlled, double-blind clinical trials of up to 6 weeks duration involving 1038 patients (684 amlodipine besylate, 354 placebo) with chronic stable angina. In 5 of the 8 studies significant increases in exercise time (bicycle or treadmill) were seen with the 10 mg dose. Increases in symptom-limited exercise time averaged 12.8% (63 sec) for amlodipine besylate 10 mg, and averaged 7.9% (38 sec) for amlodipine besylate 5 mg. Amlodipine besylate 10 mg also increased time to 1 mm ST segment deviation in several studies and decreased angina attack rate. The sustained efficacy of amlodipine besylate 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, amlodipine besylate therapy decreased attacks by approximately 4/week compared with a placebo decrease of approximately 1/week (p less than 0.01). Two of 23 amlodipine besylate and 7 of 27 placebo patients discontinued from the study due to lack of clinical improvement.

#### Studies in Patients with Congestive Heart Failure:

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

Another study (PRAISE-2) randomized patients with NYHA class III (80%) or IV (20%) heart failure without clinical symptoms or objective evidence of underlying ischemic disease, on stable doses of

ACE inhibitor (99%), digitalis (99%) and diuretics (99%), to placebo (n=827) or amlodipine besylate (n=827) and followed them for a mean of 33 months. There was no statistically significant difference between amlodipine besylate and placebo in the primary endpoint of all cause mortality (95% confidence limits from 8% reduction to 29% increase on amlodipine besylate). With amlodipine besylate there were more reports of pulmonary edema.

## INDICATIONS AND USAGE

### 1. Hypertension

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

### 2. Coronary Artery Disease

#### Chronic Stable Angina

Amlodipine besylate is indicated for the symptomatic treatment of chronic stable angina.

Amlodipine besylate may be used alone or in combination with other antianginal agents.

#### Vasospastic Angina (Prinzmetal's or Variant Angina)

Amlodipine besylate is indicated for the treatment of confirmed or suspected vasospastic angina.

Amlodipine besylate may be used as monotherapy or in combination with other antianginal drugs.

## CONTRAINDICATIONS

Amlodipine besylate 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 amlodipine besylate is gradual in onset, acute hypotension has rarely been reported after oral administration. Nonetheless, caution as with any other peripheral vasodilator, should be exercised when administering amlodipine besylate, 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. Amlodipine besylate (5 to 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). Amlodipine besylate 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:** Amlodipine besylate 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 amlodipine besylate is extensively metabolized by the liver and the plasma elimination half-life ( $t_{1/2}$ ) is 56 hours in patients with impaired hepatic function, caution should be exercised when administering amlodipine besylate to patients with severe hepatic impairment.

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

**Effect of other agents on Amlodipine besylate.**

**CIMETIDINE:** Co-administration of amlodipine besylate with cimetidine did not alter the pharmacokinetics of amlodipine besylate.

**GRAPEFRUIT JUICE:** Co-administration of 240 mL of grapefruit juice with a single oral dose of amlodipine 10 mg in 20 healthy volunteers had no significant effect on the C<sub>6</sub>H<sub>6</sub>O<sub>3</sub>S pharmacokinetics of amlodipine.

**MAALOX (antacid):** Co-administration of the antacid Maalox with a single dose of amlodipine besylate had no significant effect on the pharmacokinetics of amlodipine besylate.

**SILDENAFIL:** A single 100 mg dose of sildenafil (Viagra®) in subjects with essential hypertension had no effect on the pharmacokinetic parameters of amlodipine besylate. When amlodipine besylate and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

**Effect of Amlodipine besylate on other agents.**

**ATORVASTATIN:** Co-administration of multiple 10 mg doses of amlodipine besylate with 80 mg of atorvastatin resulted in no significant change in the steady state pharmacokinetic parameters of atorvastatin.

**DIGOXIN:** Co-administration of amlodipine besylate with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers.

**ETHANOL (alcohol):** Single and multiple 10 mg doses of amlodipine besylate had no significant effect on the pharmacokinetics of ethanol.

**WARFARIN:** Co-administration of amlodipine besylate with warfarin did not change the warfarin prothrombin response time.

In clinical trials, amlodipine besylate has been safely administered with thiazide diuretics, betablockers, 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 maleate in the diet for up to two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 amlodipine mg/kg/day showed no evidence of a carcinogenic effect of the drug. For the mouse, the highest dose was, on a mg/m<sup>2</sup> basis, similar to the maximum recommended human dose of 10 mg amlodipine/day\*). For the rat, the highest dose, was on a mg/m<sup>2</sup> basis, about twice the maximum recommended human dose\*.

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

There was no effect on the fertility of rats treated orally with amlodipine maleate (males for 64 days and females for 14 days prior to mating) at doses up to 10 mg amlodipine/kg/day (8 times\* the maximum recommended human dose of 10 mg/day on a mg/m<sup>2</sup> basis).

**Pregnancy Category C:** No evidence of teratogenicity or other embryo/fetal toxicity was found when

pregnant rats and rabbits were treated orally with amlodipine maleate at doses up to 10 mg amlodipine/kg/day (respectively 8 times\* and 23 times\* the maximum recommended human dose of 10 mg on a mg/m<sup>2</sup> 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 receiving amlodipine maleate at a dose equivalent to 10 mg amlodipine/kg/day for 14 days before mating and throughout mating and gestation. Amlodipine maleate has been shown to prolong both the gestation period and the duration of labor in rats at this dose. 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.

\*Based on patient weight of 50 kg.

**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 amlodipine besylate is administered.

**Pediatric Use:** The effect of amlodipine besylate on blood pressure in patients less than 6 years of age is not known.

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

#### ADVERSE REACTIONS

Amlodipine besylate has been evaluated for safety in more than 11,000 patients in U.S. and foreign clinical trials. In general, treatment with amlodipine besylate was well-tolerated at doses up to 10 mg daily. Most adverse reactions reported during therapy with amlodipine besylate were of mild or moderate severity. In controlled clinical trials directly comparing amlodipine besylate (N=1730) in doses up to 10 mg to placebo (N=1250), discontinuation of amlodipine besylate 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 mg N=296	10 mg N=268	Placebo N=520
Edema	1.8	3	10.8	0.6
Dizziness	1.1	3.4	3.4	1.5
Flushing	0.7	1.4	2.6	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% in placebo-controlled clinical trials include the following:

Placebo-Controlled Studies	AMLODIPINE BESYLATE (%) (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:

Adverse Event	AMLODIPINE BESYLATE		PLACEBO	
	Male=% (N=1218)	Female=% (N=512)	Male=% (N=914)	Female=% (N=336)
Edema	5.6	14.6	1.4	5.1
Flushing	1.5	4.5	0.3	0.9
Palpitations	1.4	3.3	0.9	0.9
Somnolence	1.3	1.6	0.8	0.3

The following events occurred in less than 1% but greater than 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, vasculitis.

Central and Peripheral Nervous System: hypoesthesia, neuropathy peripheral, paresthesia, tremor, vertigo.

Gastrointestinal: anorexia, constipation, dyspepsia,\*\* dysphagia, diarrhea, flatulence, pancreatitis, vomiting, gingival hyperplasia.

General: allergic reaction, asthenia,\*\* back pain, hot flushes, malaise, pain, rigors, weight gain, weight decrease.

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: angioedema, erythema multiforme, 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: hyperglycemia, thirst.

Hemopoietic: leukopenia, purpura, thrombocytopenia.

The following events occurred in less than 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.

Amlodipine besylate 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 or hepatitis) in some cases severe enough to require hospitalization have been reported in association with use of amlodipine.

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

#### OVERDOSAGE

Single oral doses of amlodipine maleate equivalent to 40 mg amlodipine/kg and 100 mg amlodipine/kg in mice and rats, respectively, caused deaths. Single oral amlodipine maleate doses equivalent to 4 or more mg amlodipine/kg or higher in dogs (11 or more times the maximum recommended human dose on a mg/m<sup>2</sup> basis) 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 amlodipine besylate 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 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 amlodipine besylate is highly protein bound, hemodialysis is not likely to be of benefit.

#### DOSAGE AND ADMINISTRATION

Adults: The usual initial antihypertensive oral dose of amlodipine besylate 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 amlodipine besylate 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 to 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.

The recommended dose range for patients with coronary artery disease is 5 to 10 mg once daily. In clinical studies the majority of patients required 10 mg (see CLINICAL PHARMACOLOGY, Clinical studies).

Children: The effective antihypertensive oral dose in pediatric patients ages 6-17 years is 2.5 mg to 5 mg once daily. Doses in excess of 5 mg daily have not been studied in pediatric patients. See CLINICAL PHARMACOLOGY.

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

#### HOW SUPPLIED

Amlodipine besylate 2.5 mg Tablets (amlodipine besylate, USP equivalent to 2.5 mg of amlodipine per tablet) are supplied as white, round, flat-faced, beveled edged tablets debossed with IG on one side and 237 on the other and supplied as follows:

NDC 31722-237-90 Bottle of 90  
NDC 31722-237-10 Bottle of 1000

Amlodipine besylate 5 mg Tablets (amlodipine besylate, USP equivalent to 5 mg of amlodipine per tablet) are supplied as white, round, flat-faced, beveled edged tablets debossed with IG on one side and 238 on the other and supplied as follows:

NDC 31722-238-90 Bottle of 90  
NDC 31722-238-10 Bottle of 1000

Amlodipine besylate 10 mg Tablets (amlodipine besylate, USP equivalent to 10 mg of amlodipine per tablet) are supplied as white, round, flat-faced, beveled edged tablets debossed with IG on one side and 239 on the other and supplied as follows:

NDC 31722-239-90 Bottle of 90  
NDC 31722-239-10 Bottle of 1000

Manufactured by:  
InvaGen Pharmaceuticals, Inc  
Hauppauge, NY 11788

Manufactured for:  
Camber Pharmaceuticals, Inc.  
Piscataway, NJ 08854

Rev : 09/07

Store at 20°-25°C (68°-77°F). [See USP Controlled Room Temperature].

**Hypertensa™ PRODUCT INFORMATION** Hypertensa (U.S. patent pending) capsules by oral administration. A specially formulated Medical Food product, consisting of a proprietary blend of amino acids and polyphenol ingredients in specific proportions, for the dietary management of the metabolic processes associated with hypertension (HT). Must be administered under physician supervision. Medical Foods Medical Food products are often used in hospitals (e.g., for burn victims or kidney dialysis patients) and outside of a hospital setting under a physician's care (e.g., for PKU, AIDS patients, cardiovascular disease, sleep disorders) for the dietary management of diseases in patients with particular medical or metabolic needs due to their disease or condition. Congress defined "Medical Food" in the Orphan Drug Act and Amendments of 1988 as "a system which is formulated to be consumed or administered enterally [or orally] under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation." Medical Foods are complex formulated products, requiring sophisticated and exacting technology. Hypertensa has been developed, manufactured, and labeled in accordance with both the statutory and the FDA regulatory definition of a Medical Food. Hypertensa must be used while the patient is under the ongoing care of a physician. **HYPERTENSION (HT)** HT as a Metabolic Deficiency Disease A critical component of the definition of a Medical Food is the requirement for a distinctive nutritional deficiency. FDA scientists have proposed a physiologic definition of a distinctive nutritional deficiency as follows: "the dietary management of patients with specific diseases requires, in some instances, the ability to meet nutritional requirements that differ substantially from the needs of healthy persons. For example, in establishing the recommended dietary allowances for general, healthy population, the Food and Nutrition Board of the Institute of Medicine National Academy of Sciences, recognized that different or distinctive physiologic requirements may exist for certain persons with "special nutritional needs arising from metabolic disorders, chronic diseases, injuries, premature birth, other medical conditions and drug therapies. Thus, the distinctive nutritional needs associated with a disease reflect the total amount needed by a healthy person to support life or maintain homeostasis, adjusted for the distinctive changes in the nutritional needs of the patient as a result of the effects of the disease process on absorption, metabolism and excretion." It was also proposed that in patients with certain disease states who respond to nutritional therapies, a physiologic deficiency of the nutrient is assumed to exist. For example, if a patient with hypertension responds to an arginine formulation by decreasing the blood pressure, a deficiency of arginine is assumed to exist. Patients with hypertension are known to have nutritional deficiencies of arginine, choline, flavonoids, and certain antioxidants. Patients with hypertension frequently exhibit reduced plasma levels of arginine and have been shown to respond to oral administration of an arginine formulation. Research has shown that arginine reduced diets result in a fall of circulating arginine. Patients with hypertension have activation of the arginase pathway that diverts arginine from the production of nitric oxide to production of deleterious nitrogen molecules such as peroxynitrite leading to a reduced level of production of nitric oxide for a given

arginine blood level. Research has also shown that a genetic predisposition can lead to increased arginine requirements in certain patients with hypertension. Arginine is required to fully potentiate nitric oxide synthesis by the arterioles. A deficiency of arginine leads to reduced nitric oxide production by the arterioles. Low fat diets, frequently used by patients with hypertension, are usually arginine deficient. Flavonoids potentiate the production of nitric oxide by the arterioles thereby reducing blood pressure in hypertensive patients. Low fat diets and diets deficient in flavonoid rich foods result in inadequate arginine and flavonoid concentrations, impeding nitric oxide production in certain patients with hypertension. Provision of arginine, choline, and flavonoids with antioxidants, in the correct proportions can restore the production of beneficial nitric oxide, thereby reducing blood pressure.

**PRODUCT DESCRIPTION** Primary Ingredients Hypertensa consists of a proprietary blend of amino acids, cocoa, cinnamon and flavonoids in specific proportions. These ingredients fall into the category of "Generally Regarded as Safe" (GRAS) as defined by the Food and Drug Administration (FDA) (Sections 201(s) and 409 of the Federal Food, Drug, and Cosmetic Act). A GRAS substance is distinguished from a food additive on the basis of the common knowledge about the safety of the substance for its intended use. The standard for an ingredient to achieve GRAS status requires not only technical demonstration of non-toxicity and safety, but also general recognition of safety through widespread usage and agreement of that safety by experts in the field. Many ingredients have been determined by the U.S. Food and Drug Administration (FDA) to be GRAS, and are listed as such by regulation, in Volume 21 Code of Federal Regulations (CFR) Sections 182, 184, and 186.

**Amino Acids** Amino Acids are the building blocks of proteins. All amino acids are GRAS listed as they have been ingested by humans for thousands of years. The doses of the amino acids in Hypertensa are equivalent to those found in the usual human diet. Patients with hypertension may require an increased amount of certain amino acids that cannot be obtained from normal diet alone. Arginine, for example, is a conditional amino acid. The body can make arginine in the liver, but the liver produced arginine can only be used in the liver itself. Arginine is needed to produce nitric oxide (NO). NO is required to dilate the constricted blood vessels that are the cause of high blood pressure. Patients with hypertension have an increase in the enzyme, arginase that degrades arginine before it can be used to produce NO. Some patients with hypertension have a resistance to the use of arginine that is similar to the mechanism found in insulin resistance that is genetically determined. Patients with hypertension cannot acquire sufficient arginine from the diet without ingesting a prohibitively large amount of calories, particularly calories from protein. .

**Flavonoids** Flavonoids are a group of phytochemical compounds found in all vascular plants including fruits and vegetables. They are a part of a larger class of compounds known as polyphenols. Many of the therapeutic or health benefits of colored fruits and vegetables, cocoa, red wine, and green tea are directly related to their flavonoid content. The specially formulated flavonoids found in Hypertensa cannot be obtained from conventional foods in the necessary proportions to elicit a therapeutic response.

**Other Ingredients** Hypertensa contains the following "inactive" or other ingredients, as fillers, excipients, and colorings: magnesium stearate, microcrystalline cellulose, Maltodextrin NF, gelatin (as the capsule material),

**Physical Description** Hypertensa is a yellow to light brown powder. Hypertensa contains L-Glutamine, L-Histadine, L-Arginine, L-Leucine, L-Cysteine, Whey Protein Hydrolysate, Choline Bitartrate, Cinnamon, Caffeine, Cocoa, Ginseng, and Grape Extract.

**CLINICAL PHARMACOLOGY** Mechanism of Action Hypertensa acts by restoring and maintaining the balance of NO in patients with hypertension.

**Metabolism** The amino acids in Hypertensa are primarily absorbed by the stomach and small intestines. All cells metabolize the amino acids in Hypertensa.

**Circulating arginine and choline blood levels** determine the production of NO and acetylcholine.

**Excretion** Hypertensa is not an inhibitor of cytochrome P450 1A2, 2C9, 2C19, 2D6, or 3A4. These isoenzymes are principally responsible for 95% of all detoxification of drugs, with CYP3A4 being responsible for detoxification of roughly 50% of drugs. Amino acids do not appear to have an effect on drug metabolizing enzymes.

**INDICATIONS FOR USE** Hypertensa is intended for the clinical dietary management of the metabolic

processes in patients with hypertension.

**CLINICAL EXPERIENCE** Administration of Hypertensa has demonstrated significant functional improvements in blood pressure when used for the dietary management of the metabolic processes associated with hypertension. Administration of Hypertensa results in the reduction of blood pressure in hypertensive patients. Hypertensa has no effect on normal blood pressure.

**PRECAUTIONS AND CONTRAINDICATIONS** Hypertensa is contraindicated in an extremely small number of patients with hypersensitivity to any of the nutritional components of Hypertensa.

**ADVERSE REACTIONS** Oral supplementation with L-arginine at high doses up to 15 grams daily is generally well tolerated. The most commonly reported adverse reactions at higher doses — from 15 to 30 grams daily — are nausea, abdominal cramps, and diarrhea. Some patients may experience these symptoms at lower doses. The total combined amount of amino acids in each Hypertensa capsule does not exceed 400 mg.

**DRUG INTERACTIONS** Hypertensa does not directly influence the pharmacokinetics of prescription drugs. Clinical experience has shown that administration of Hypertensa may allow for lowering the dose of co-administered drugs under physician supervision. **POST-MARKETING SURVEILLANCE** Post-marketing surveillance has shown no serious adverse reactions. Reported cases of mild rash and itching may have been associated with allergies to Hypertensa flavonoid ingredients, including cocoa and chocolate. The reactions were transient in nature and subsided within 24 hours.

**OVERDOSE** There is a negligible risk of overdose with Hypertensa as the total dosage of amino acids in a one month supply (90 capsules) is less than 36 grams. Overdose symptoms may include diarrhea, weakness, and nausea.

**DOSAGE AND ADMINISTRATION** Recommended Administration For the dietary management of the metabolic processes associated with hypertension. Take (2) capsules once or twice daily, as directed by physician. As with most amino acid formulations Hypertensa should be taken without food to increase the absorption of key ingredients.

**How Supplied** Hypertensa is supplied in green and white, size 0 capsules in bottles of 60 and 90 capsules. **Physician Supervision** Hypertensa is a Medical Food product available by prescription only, and must be used while the patient is under ongoing physician supervision. U.S. patent pending. Manufactured by Arizona Nutritional Supplements, Inc. Chandler AZ 85225 Distributed by Physician Therapeutics LLC, Los Angeles, CA 90077. [www.ptlcentral.com](http://www.ptlcentral.com) © Copyright 2003-2006, Physician Therapeutics LLC, all rights reserved NDC: 68405-1007-02 NDC: 68405-1007-03

**Storage** Store at room temperature, 59-86OF (15-30OC) Protect from light and moisture. Hypertensa is supplied to physicians in a recyclable plastic bottle with a child-resistant cap.

**PHYSICIAN THERAPEUTICS HYPERTENSA** Medical Food Rx only 90 Capsules Directions for use: Must be administered under physician supervision. For adults only. As a Medical Food, take two (2) capsules four times daily in between meals or as directed by physician. For the dietary management of hypertension. Contains no added sugar, starch, wheat, yeast, preservatives, artificial flavor. Storage: Keep tightly closed in a cool dry place 8-320 C (45-900F), relative humidity, below 50%. Warning: Keep this product out of the reach of children. NDC# 68405-1007-03 Ingredients: Each serving (per 2 capsules) contains: Proprietary Amino Acid Blend L-Glutamine L-Histadine, L-Arginine, L-Leucine, L-Cysteine, Whey Protein Hydrolysate, Choline Bitartrate, Cinnamon (bark), Caffeine, Cocoa(6% Theobromine) (fruit), Ginseng, Grape Extract (20% Polyphenol) (seed) other indgredients: Tricalcium phosphate, gelatin, silicon dioxide, vegetable magnesium stearate, microcrystalline cellulose, chlorophyllin copper complex, titanium dioxide. Distributed exclusive by: A Division of Targeted Medical Pharma, Inc Los Angeles, CA 90077 [www.ptlcentral.com](http://www.ptlcentral.com) Patent Pending.

For the Dietary Management of Hypertension. Two capsules twice daily or as directed by physician. See product label and insert. Hypertensa Medical Food **PHYSICIAN THERAPEUTICS**  
Hypertensa + Amlodipine 2.5 mg A Convenience Packed Medical Food and Drug Hypertenipine-

2.5 PHYSICIAN THERAPEUTICS > Hypertensa 90 Capsuled > Amlodipine 2.5 mg 30 Tablets No Refills Without Physician Authorization Rx Only NDC# 68405-037-36 of this co-pack As prescribed by physician. See product label and product information insert. Amlodipine 2.5 mg Rx Drug



68405-1007-03

**Directions for use:**  
**Must be administered under physician supervision.**

For adults only. As a Medical Food, take two (2) capsules twice daily in between meals or as directed by physician.

**For the dietary management of hypertension.**

Contains no added sugar, starch, wheat, yeast, preservatives, artificial flavor.

**Storage:**  
 Keep tightly closed in a cool dry place 8-32°C (45-90°F), relative humidity, below 50%.

**Warning: Keep this product out of the reach of children.**

NDC# 68405-1007-03



## HYPERTENSA

Medical Food

Rx only

90 Capsules

**Ingredients:**  
 Each serving (per 2 capsules) contains:  
 Proprietary Amino Acid Blend  
 L-Glutamine, L-Histidine, L-Arginine, L-Leucine, L-Cysteine, Whey Protein Hydrolysate,  
 Choline Bitartrate,  
 Cinnamon (bark),  
 Caffeine,  
 Cocoa (6% Theobromine) (fruit),  
 Ginseng,  
 Grape Extract (20% Polyphenol) (seed)

**Other Ingredients:** Tricalcium phosphate, gelatin, silicon dioxide, vegetable magnesium stearate, microcrystalline cellulose, chlorophyllin copper complex, titanium dioxide.

**Distributed exclusively by:**  
 Physicians Therapeutics LLC  
 A Division of Targeted Medical Pharma, Inc.  
 Los Angeles, CA 90077  
 www.ptcentral.com  
 Patent Pending

52959-0910-30

AMLODIPINE BESYLATE 2.5mg TABLET

Lot #: APN00QE #30

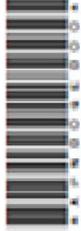
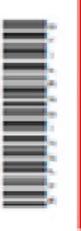
Mfg: CAMBER PHM

Exp: 06/11 Compare to: Norvasc

Mfg. NDC: 31722-0237-10

CAUTION: Federal law PROHIBITS the transfer of this drug to anyone other than the person to whom prescribed and prohibits dispensing without a prescription unless OTC. See insert for additional info. KEEP OUT OF REACH OF CHILDREN. Store in a cool dry place at 68 to 77 degrees F.

Take as directed by your Doctor or See insert for usual dosage information

AMLODIPINE BESYLATE 2.5mg TABLET			
52959-0910-30	Qty	#30	
06/11		Lot APN00QE	
Norvasc		31722-0237-10	

AMLODIPINE BESYLATE 2.5mg TABLET			
52959-0910-30	Qty	#30	
06/11		Lot APN00QE	
Norvasc		31722-0237-10	

AMLODIPINE BESYLATE 2.5mg TABLET			
52959-0910-30	Qty	#30	
06/11		Lot APN00QE	
Norvasc		31722-0237-10	

AMLODIPINE BESYLATE 2.5mg TABLET			
52959-0910-30	Qty	#30	
06/11		Lot APN00QE	
Norvasc		31722-0237-10	

Regain: FU Harkins Co., Inc. Newport, CA 95444

**A Convenience Packed Medical Food & Drug**

# **Hypertenipine-2.5<sup>TM</sup>**



- ▶ **Hypertensa<sup>TM</sup> 90 Capsules**
- ▶ **Amlodipine 2.5 mg 30 Tablets**

No Refills Without  
Physician Authorization

**Rx Only**  
NDC# 68405-037-36  
*of this co-pack*

## **HYPERTENIPINE**

amlodipine besylate, arginine kit

### **Product Information**

**Product Type**

HUMAN PRESCRIPTION DRUG

**Item Code (Source)**

NDC:68405-037

**Packaging**

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68405-037-36	1 in 1 KIT		

**Quantity of Parts**

Part #	Package Quantity	Total Product Quantity
Part 1	1 BOTTLE	30
Part 2	1 BOTTLE	90

**Part 1 of 2****AMLODIPINE BESYLATE**

amlodipine besylate tablet

**Product Information**

Item Code (Source)	NDC:52959-910(NDC:31722-237)
Route of Administration	ORAL

**Active Ingredient/Active Moiety**

Ingredient Name	Basis of Strength	Strength
AMLODIPINE BESYLATE (UNII: 864V2Q084H) (AMLODIPINE - UNII:1J444QC288)	AMLODIPINE BESYLATE	2.5 mg

**Inactive Ingredients**

Ingredient Name	Strength
CELLULOSE, MICROCRYSTALLINE (UNII: OPIR32D61U)	
ANHYDROUS, DIBASIC CALCIUM PHOSPHATE (UNII: L11K75P92J)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	

**Product Characteristics**

Color	white (WHITE)	Score	no score
Shape	ROUND	Size	6mm
Flavor		Imprint Code	IG;237
Contains			

**Packaging**

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:52959-910-30	30 in 1 BOTTLE		

## Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA077955	07/07/2011	

## Part 2 of 2

### HYPERTENSA

arginine capsule

## Product Information

Route of Administration ORAL

## Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ARGININE (UNII: 94ZLA3W45F) (ARGININE - UNII:94ZLA3W45F)	ARGININE	90 mg

## Inactive Ingredients

Ingredient Name	Strength
MAGNESIUM STEARATE (UNII: 70097M6I30)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
MALTODEXTRIN (UNII: 7CVR7L4A2D)	
GELATIN (UNII: 2G86QN327L)	

## Product Characteristics

Color	white (WHITE)	Score	no score
Shape	CAPSULE	Size	21mm
Flavor		Imprint Code	;
Contains			

## Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1		90 in 1 BOTTLE		

## Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
Medical Food		07/07/2011	

## Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
unapproved drug other		07/07/2011	

**Labeler** - Physician Therapeutics LLC (931940964)

### Establishment

Name	Address	ID/FEI	Business Operations
InvaGen Pharmaceuticals, Inc		165104469	manufacture

### Establishment

Name	Address	ID/FEI	Business Operations
H.J. Harkins Company, Inc.		147681894	repack

### Establishment

Name	Address	ID/FEI	Business Operations
Targeted Medical Pharma, Inc.		126962740	manufacture

Revised: 8/2011

Physician Therapeutics LLC