HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use amlodipine besylate tablets safely and effectively. See full prescribing information for amlodipine besylate tablets.

Amlodipine Besylate Tablets, USP for oral administration Initial U.S. Approval: 1987 -- INDICATIONS AND USAGE -

Hypertension (1.1)

 Hypertension (1.1)

 Amlodipine besylate tablet Lowering blood pressure in and myocardial infarctions
 Coronary Artery Diseases (1.2)

 Chronic Stable Angina
 Vasospastic Angina (Prinzr

 esylate tablets are indicated for the treatment of hypertension, to lower blood pressure. Id pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes

- Vesspastic Angina (Prinzmetal's or Variant Angina)
 Angiographicula Courameted Coronary Artery Disease in patients without heart failure or an ejection fraction <40%.

- DOSAGE AND ADMINISTRATION -- Adult rec ecommended starting dose: 5 mg once daily with maximum dose 10 mg once daily. (2.1) mall, fragile, or elderly patients, or patients with hepatic insufficiency may be started on 2.5 mg once daily.

- (2.1) Pediatric starting dose: 2.5 mg to 5 mg once daily. (2.2)
- Important Limitation: Doses in excess of 5 mg daily have not been studied in pediatric patients. (2.2)
- OSAGE FORMS AND STRENGTHS --- 2.5 mg, 5 mg, and 10 mg Tablets (3)

- FULL PRESCRIBING INFORMATION: CONTENTS* 1 INDICATIONS AND USAGE 1.2 Coronary Artery Disease (CAD) **2 DOSAGE AND ADMINISTRATION** 2.1 Adults 2.1 Auuns 2.2 Children 3 DOSAGE FORMS AND STRENGTHS 5 WARNINGS AND PRECAUTIONS 5.1 Hypotension 5.2 Increased Angina or Myocardial Infarction 5.3 Patients with Henatic Eailure 6 ADVERSE REACTIONS
- 6.1 Clinical Trials Experience 6.2 Postmarketing Experienc 7 DRUG INTERACTIONS 7.1 In Vitro Date 7.2 Cimetidine 7.3 Grapefruit Juice 7.4 Magnesium and 7.5 Sildenafil and Aluminum Hydroxide Antacid 7.6 Atorvastatin 7.7 Simvastatin 7.7 Sinvusiani 7.8 Digoxin 7.9 Ethanol (Alcohol) 7.10 Warfarin 7.11 CYP3A4 Inhibitors 7.12 CYP3A4 Inducers

Revised 09/2013

(Epic)

Tablets, USI

for oral administration

dipine Besylate

FULL PRESCRIBING INFORMATION 1.1

NIONS AND USAVE Hypertension Amidipine besylate tablets are indicated for the treatment of hypertension, to lower blood pressure. Lowering blood pressure educes the risk of fratal and nonfratal cardiovascular events, primarily stroke and myocardial infractions. These benefits have been seen in controlled trials of antihypertensive drug from a wide variety of pharmacologic classes including amiddipine besylate.

trion a Wide vaniery or promotioogie crosses incruding uninoquiene expressive. Control of high blood pressure should be part of comprehensive cardiovscular risk management, including, as apportisel, bjird cantol, diabetes management, anthhombatic therapy, smaking cessation, exercise, and limited softwin intoke. Many patients will require more than one drug to achieve blood pressure goals. For specific dovice on goals and management, see published guideline such as those of the Notional High Blood Pressure Education Progent's Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (INC).

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

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

Tower invour pressure you. Some antihypertensive drugs have smaller blood pressure effects (as monotherapy) in black patients, and many onthypertensive drugs have additional opproved indications and effects (e.g., on angina, heart failure, or diabetic kidney disease). These considerations may guide selection of therapy. Amlodipine besylate tablets may be used alone or in combination with other antihypertensive agents.

1.2 Coronary Artery Disease (CAD) <u>Chronic Stable Angina</u> Amologine besylate tablets are indicated for the symptomatic treatment of chronic stable angina. Amologine besylate tablets may be used alone or in combination with other antianginal agents.

<u>Vassepastic Angina (Prinzmetal's or Variant Angina)</u> Amlodipine besylate tablets are indicated for the treatment of confirmed or superted vassepastic angina. Amlodipine besylate tablets may be used as mono combination with other antionginal agents.

Angiographically Documented CAD In patients with recently documented CAD by angiography and without heart failure or fraction ~40%, amlodipine besylate tablets are indicated to reduce the risk of hospita angina and to reduce the risk of a coronary reversal/arization procedure.

2 DOSAGE AND ADMINISTRATION 2.1 Adults

Adults The usual initial antihypertensive oral dose of amlodipine besylate tablets is 5 mg once daily, and the The usual initial an imperiences of an access of an adoptine besynaer radies is 5 mg once adary, and me maximum dose is 10 mg once daily. Small, fragile, or elderly patients, or patients with hepatic insufficiency may be started on 2.5 mg once daily and this dose may be used when adding amlodipine besylate tablets to other antihypertensive

Adjust dosage according to bload pressure goals. In general, writ 7 to 14 days between firstinion steps. Tirate more rapidly, however, if clinically warranted, provided the patient is assessed frequently. Angina: The recommended dose for chronic stable or vasospassiic 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. Coromar artery disease: The recommended dose range for patients with coronary artery disease is 5–10 mg one daily. In clinical studies, the majority of patients required 10 mg [see Clinical Studies (14.4]).

- 2.2 Children The effective anthypertensive and dase in pediatric patients ages 6–17 years is 2.5 mg to 5 mg once daily. Dases in excess of 5 mg daily have not been studied in pediatric patients [see Clinical Pharmacology (12.4), Clinical Studies (14.1)].

3 DOSAGE FORMS AND STRENGTHS 2.5.5 and 10 mg Tablets

- 4 CONTRAINDICATIONS Amlodipine besylate tablets of are contraindicated in patients with known sensitivity to amlodiping
- 5 WARNINGS AND PRECAUTIONS 5.1
- Hypotension Symptomatic hypotension is possible, particularly in patients with severe aartic stenosis. Because of the aradual onset of action, acute hypotension is unlikely. 5.2 Increased Angina or Myocardial Infarction Worsening angina and acute myocardial infarction can develop after starting or increasing the dose of amlodipine besylate tablets, particularly in patients with severe obstructive coronary artery disease.
- 5.3 Patients with Hepatic Failure Because and objaine besylate tables are extensively metabolized by the liver and the plasma elimination half-life (h₂) is 56 hours in patients with impoired hepatic function, titrate slowly when administering amlodipine besylate tables to patients with sevene hepatic impairment.

6 ADVERSE REACTIONS 6.1 Clinical Trials Experience Because clinical trials are cond

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

the dirical traits of a drug cannot be directly compares to rates in me cannot mass or anonner using unua many not reflect the rates observed in practica. Amologine besylate tablets have been evaluated for sofety in more than 11,000 patients in U.S. and foreign clinical triads. In general, treatment with amologine besylate tablets was well-tolerated at doses up to 10 mg daily. Most adverse reactions reported during therapy with amologine besylate tablets were of mild or moderate severity. In controlled clinical triads directly comparing amologine besylate tablets tablets (W-1200) at doses up to 10 mg for placebo. (W-1250), discontinuation of amologine besylate tablets because of adverse reactions was required in only about 1.5% of patients and was not

-- CONTRAINDICATIONS --• Known sensitivity to amlodipine (4)

- Symptomatic hypotension is possible, particularly in patients with severe cortic stenasis. However, acute hypotension is unlikely. (5.1)
- unrestry (2,1)
 Worsening angina and acute myocardial infarction can develop after starting or increasing the dose of amlodipine besyltate tablets, particularly in patients with severe obstructive coronary artery disease. (5.2)
 Tirate slowly in patients with severe hepatic impairment. (5.3)

To report SUSPECTED ADVERSE REACTIONS, contact Epic Pharma at 1-888-374-2791 or www.epicpharma.com or FDA at 1-800-FDA-1088 or <u>www.fda.gov/medwatch</u>.

---- DRUG INTERACTIONS ---Do not exceed doses greater than 20 mg daily of simulatation. (7.1)

Pregnancy: Use only if the potential benefit justifies the risk. (8.1)
 Wursing: Discontinue when administering amildigine besylart toldets. (8.3)
 Pediatric: Effect an pottentisk sts than dynamo (8.4)
 Geriatric: Start dosing at the low end of the dose range. (8.5)

Revised: September 2013



*Sections or subsections omitted from the full prescribing information are not listed

significantly different from placebo (about 1%). The most commonly reported side effects more frequent than placebo are reflected in the table below. The incidence (%) of side effects that occurred elated manner is as follo

	2.5 mg N=275	5 mg N=296	10 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 reactions that were not clearly dose related but were reported with an incidence greater than 1.0% in placebo-controlled clinical trials include the following:

Amladinina Paculata (%)

	(N=1730)	(N=1250)
Fatigue	4.5	2.8

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: Amlodinine Resultate Placeho

	Amioalpine Besylate		riacebo		prosso	
	Male=% (N=1218)	Female=% (N=512)	Male=% (N=914)	Female=% (N=336)	includi unresp	
Edema	5.6	14.6	1.4	5.1	phenyl highly	
Flushing	1.5	4.5	0.3	0.9	11 DESCRIPTION	
Palpitations	1.4	3.3	0.9	0.9	Amlod	
Somnolence	1.3	1.6	0.8	0.3		
		but >0.1% of patients in			Amlod 4-(2-ch	

conditions of open trials or marketing experience where a causal listed to alert the physician to a possible relationship: Cardiovascular: arhythmia (including ventricular tadaycardia and atrial fibrillation), bradycardia, chest pain, peripheral ischemia, syncope, tadhycardia, vasculhis. Central and Peripheral Nervous System: hypoesthesia, neuropathy peripheral, paresthesia,

tremor, vertiga. Gastrointestinal: anorexia, constipation, dysphagia, diarrhea, flatulence, pancreatitis, vomiting, General: allergic reaction, asthenia,¹ back pain, hot flushes, malaise, pain, rigors, weight gain,

weight decrease. Musculoskeletal System: arthralgia, arthrasis, muscle cramps,¹ myalgia. Psychiatric: sexual dysfunction (male¹ and female), insomnia, nervousness, depression, abnormal

dreams, anxiety, depersonalization. Respiratory System: dyspnea, ¹ epistaxis. Skin and Appendages: angioedema, erythema multiforme, pruritus, ¹ rash, ¹ rash erythematous,

Skin and Appendages: angioedema, eryfhema multhorme, pruntus,¹ tost rosh maculopapular. Special Senses: abnornal vision, conjunctivitis, djalopia, eye pain, tinnitus. Urinary System: micharitoin fequency, micharitian disader, nochria. Autonomic Nervous System: dy mouth, sweating increased. Metabolic and Nutritional: hyperglycemia, thirst. Hemopoletic: leukopenia, purpura, thrombacytopenia.

 $^1\mathrm{These}$ events accurred in less than 1% in placeba-controlled trials, but the incidence of these side effects was between 1% and 2% in all multiple dose studies.

Amlodipine besylate therapy has not been associated with clinically significant changes in routin laboratory tests. No clinically relevant changes were noted in serum potassium, serum glucose, t

halobaratory tests. No clinically relevant changes were noted in serum potassium, serum glu triglycerides, total cholesterol, HDL cholesterol, uric acid, blood urea nitrogen, or creatinine

- In the CAMELOT and PREVENT studies [see *Clinical Studies* (14.4)], the adverse event profile was similar to that reported previously (see above), with the most common adverse event being peripheral
- 6.2 Portmarketing Experience Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to day exposure. protection to reasting remains requery or sciencific decomposition of the providence of the following parameterization of the providence of the following parameterization of the providence of Amlodipine besylate tablets have been used safely in patients with chronic obstructiv disease, well-compensated congestive heart failure, coronary artery disease, peripher disease, diabetes mellitus, and abnormal lipid profiles. nary artery disease, peripheral vascular

7 DRUG INTERACTIONS

7.1 In Vitro Data

- ate that amlodipine besylate tablets have no effect on the human plasma protein
- 7.2 Cimetidine Co-administration of amladipine besylate tablets with cimetidine did not alter the pharmacokinetics of amlodipine besylate.
- 7.3 Grapheni Juce Coordininistration of 240 mL of grapefruit juice with a single oral dose of amlodipine 10 mg in 20 healthur valunteers had no significant effect on the pharmacokinetics of amlodipine.
- 7.4 Magnesium and Aluminum Hydroxide Antacid Co-administration of a magnesium and aluminum hydroxide antacid with a single dose of amlodipine besylate tablets had no significant effect on the pharmacokinetics of amlodipine besylate tablets.

- 7.5 Sidenafil A single 100 mg dose of sidenafil in subjects with essential hypertension had no effect on the pharmacokinetic parameters of amlodipine besylate tablets. When amlodipine besylate tablets and sidenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

lead to clinically significant changes in heart rate or blood pressures in normotensive patients with

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

In hypertensive potients with normal renal function, therapeutic doses of amlodpine 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.

rend picture to without dange in hittotion traction or proteinuna. As with other colcium channel blockes, hemodynamic measurements of cardiac function at rest and during exercise (a pocing) in potients with normal ventricular function treated with aniodipine besylate have generally demonstrated a small increase in cardiac index without significant influence on dig/1 at on elf wentricular and distation (pressure or volume. In hemodynamic studies, annologine 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 bete-blockers to man. Similar inflindings, however, have been observed in normal or well-compressible patients with heart failure with agents possessing significant negative inotropic effects.

Electrophysiologic Effects. Annologine besylate does not change snorthal nodar hunchno or advinentirular conduction in inited ramides or man. In patients with chanois rabble engina, intravenous administration of 10 mg did not significantly after AH and HV conduction and sirus node recovery time after pacing. Similar results were obtained in patients receiving annologine besylate and concomitant beta-blockers to patients with either hypertension or angina, no adverse effects an electroardiographic parameters were observed. In chinal rulis with anging notifiest alone, and/opine besylate therapy did not after electroardiographic intervals or produce higher degrees of AV blocks.

10. There exclude any other interview of produce ingree begiets of AT anxis.
12.3 Pharmacokinetics and Metabolism After and administration of therapoultic doss of amlodigine 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 tablets is not altered by the presence of food

uru 2702. Ine ancorrumanity of anniagaine besydiate tablets is not affered by the presence of food. Amlodiptine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism with 10% of the parent compand and 60% of the metabolism secreted in the unit. *Exvio* studies have shown that approximately 93% of the circulating drug is bound to plasma proteins in hypertensive partients. Etimination from the placema is biphosix with a terminal elimination holifie of about 30-50 hours. Standy-state plasma levels of amlodiprine are reached after 7 to 8 days of consecutive daily derina.

The pharmacokinetics of amlodipine is 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 dase may be required. A similar increase in AUC was observed in patients with moderate to severe heart failure.

reatarric trahents 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.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility Rots and mice treated with amiodipine 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 amiodipine mg/kg/day, showed no evidence of a carcinogenic effect of the drug. For the mouse, the highest dose was, on a mg/m² basis, similar to the maximum recommended human dose of 10 mg amiodipine Jday.³ For the rot, the highest dose was, on a mg/m² basis, about twice the maximum recommended human dose.³

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

L trects in typertension Adult Patients: The antihypertensive efficacy of amlodipine besylate has been demonstrated in a total of 15 double-blind, placebe-controlled, randomized studies involving 800 patients on amlodipine besylate and 538 on placebe. Once duity doministation produced studies/law janking traditorebe-corrected reductions in spine and standing blood pressures at 24 hours postfoose, neuroging 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. Joerance was not demonstrated in potents studied for put to 1 year. The 3 parallel, food dose, dose response studies showed that the reduction in supine and standing blood pressures was dose-related within the recommended dosing range. Effects an distabili-pressure wave simular 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 block patients and in white patients.

Pediatric Parlients Two hundred and activenight hypertensive patients aged 6 to 17 years were randomized first to antidatione besylate 2.5 or 5 mg ance daily for 4 weeks and then randomized again to the same dose or to placeho for another 4 weeks. Patients receiving 2.5 mg or 5 mg at the end of 8 weeks had significantly lower systolic blood pressure than those secondarily randomized to placebo. The magnitude of the treatment effect is difficult to interpret, but it is probably less than 5 mmHg systolic on the 5 mg dose and 3.3 mmHg systolic on the 2.5 mg dose. Adverse events were similar to those seen in adults.

dose and 3.3 mmtg systaic on the 2.5 mg dose. Adverse events were similar to those seen in adults. **14.2 Effects in Chronic Stable Angino** The effectiveness of 5 to 10 mg/day of amlodipine besylate in exercise-induced angina has been evaluated in 8 placebo-controlled, double-blind chincla trials of up to 6 weeks duration involving 1038 patients (64 andlogine besylate) 3.54 pacebo) with charac 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 everaged 12.8% (63 sec) for amlodipine besylate 10 mg, and averaged 7.9% (43 sec) for amlodipine besylate 10 mg daso increased angina attack rate. The sustained efficiency of amlodipine besylate in angina patients has been demonstrated over long-term dosing. In patients with anging, there were no clinically significant reductions in blood pressures (4/1 mmHg) or changes in heart rate (+0.3 bpm).

14.3 Effects in Vasospastic Angina In a double-bind, placebo-controlled clinical trial of 4 weeks duration in 50 patients, amlodiprine besylate therapy decreased attacks by approximately 4/week compared with a placebo decrease of approximately 1/week (c=0.01). Two of 23 antidoptine and 7 of 27 placebo patients discontinued from the study due to lack of clinical improvement.

How the study our to lock of chinal ingrepresentation.
14.4. Effects in Documented Coronary Artery Disease In PREVENT, 825 patients with angiographically documented coronary artery disease were randomized to ambodipine besylate (5 to 10 mg ance daily) or placeba and balowed for 3 years. Although the study did not show significance on the primary objective of change in coronary luminal diameter as assessed by quantitive coronary angiography, the data suggested a forwardie autome with respect to fewer hospitalizations for angina and revascularization procedures in patients with CAD.

c) summaries arowing tangenguing, me total suggested to truthed butched Will Reget To BWell hospitalizations for original and reasons in patients with CAD.
CARELOT enrolled 1318 patients with CAD recently documented by ongiography, without left main coronary disease and without heart failure or an ejection fraction <40%. Patients (76%, males, 89% curcasia), 93% enrolled at US sites, 93% with history or angino, 25% without PCI, 44% with PCI and no steri, and 44% with a sterily area randomized to double-blind treatment with either emologine besylate (5 to 10 mg once daily) or placeba in addition to standard care that included aspinin (99%), statistic (33%), blateblockes (74%), introdyterin (50%), anti-caquiants (40%), and diuterits (32%), but addided that ciclium channel blockes. The mean duration of hollowup was 19 months. The primary endopiant sources the fullow, starker (34%), or peripheral vascutario disease. A hot of 110 (16.6%) and 152 (23.1%) first events occurred in the andiodipine besylate disease. A total of 110 (16.6%) and 152 (23.1%) first events occurred in the andiodipine besylate and placeba groups, is respectively, for a harard tario of 0.691 (95% ic 0.540-0.884, p = 0.003). The primary endopini sum of the site 1 blocks. The advisor of this starky was largely derived from the prevention of hospitalizations for heard actione of this starky was largely derived from the prevention of nositization procedures (see Table 1). Effects in various subgroups are shown in Figure 2.41</p>

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

1130 1098 Placebo

1066 1039 . .

594 # at risk

Figure 1 - Kaplan-Meier Analysis of Composite Clinical Outcomes for Amlodipine Besylate versu: Placebo

12.4 Pediatric Patients

13 NONCLINICAL TOXICOLOGY

14 CLINICAL STUDIES

14.1 Effects in Hype

Pediatric Patients

y intravascular ultras

.20

Rate 0.15

Event 0.10

0.05

8 13

Hazard Ratio=0.600 95% CI=(0.54, 0.88)

1250 1193

Electrophysiologic Effects: Amlodipine besylate does not change sinoatrial nodal function or

- 7.6 Atorvastatin Coordinistration of multiple 10 mg doses of amlodipine besylate tablets with 80 mg of atorvastatin resulted in no significant change in the steady-state pharmacokinetic parameters of atorvastatin.
- 7.7 Simvastatin Coodministration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin anompared to simvastatin alone. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily.
- 7.8 Digoxin Coadministration of amlodipine besylate tablets with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers.
- 7.9 Ethanol (Alcohol) Single and multiple 10 mg doses of amlodipine besylate tablets had no significant effect on the pharmacokinetics of ethanol. 7.10 Warfarin
 - Co-administration of amlodipine besylate tablets with warfarin did not change the warfarin prothrombin
- 7.11 CYP3A4 Inhibitors
- CYP3A4 Inhibitors Condimistration of a 180 mg daily dose of diffrazem with 5 mg amlodipine in elderly hypertensive patients resulted in a 60% increase in amlodipine systemic exposure. Erythromycin co-diministration in healthy voluntees did not significantly change amlodipine systemic exposure. However, strong inhibitors of CrP3A4 (e.g., ketoconazole, intraconazole, ritoravir) may increase the plasma concentrations of amlodipine to a greater eatent. Monitor for symptoms of hypotension and edema when amlodipine is co-administered with CrP3A4 inhibitors.
- 7.12 CYP3A4 Inducers No information is available on the quantitative effects of CYP3A4 inducers on amlodigine. Blood pressure should be closely monitored when amlodigine is co-administered with CYP3A4 inducers.
- 7.13 Cyclosporine A prospective study in renal transplant patients (N=11) showed on an average of 40% increase in trough cyclosporine levels when concomitantly treated with amlodipine.

8.3 Nursing Mothers It is not now whether amlodipine is excreted in human milk. In the absence of this information, it is recommended that nursing be discontinued while amlodipine besylate tablets are administered.

8.5 Geriartic Use Clinical studies of amlodipine besylate tablets 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, does selection for an elderly patient should be cautious, souldy starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of cancomittant disease or other drug themps. Elderly patients have decreased decrease of enablidging with a resulting increase of AUC of approximately 40–60%, and a lower initial dose may be required [see Desage and Administration (2.1)].

Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tradrycardia. In humans, experience with intentional overdosage of amlodipine besylate tablets are limited.

Single and doess of amlodipine maleate equivalent to 40 mg amlodipine/kg and 100 mg amlodipine/kg in mice and rats, respectively, cussed deaths. Single and amlodipine maleate doess equivalent to 4 or more mg amlodipine/kg ao higher in dogs (11 or more times the maximum recommended human does an a mg/m² basis) caused a marked peripheral vasadilation and

If massive overdoses should occur, initiate active cardiac and respiratory monitoring. Frequent blood pressure measurements are essential. Should hypotension occur, provide cardiovascular support including elevation of the externities and the judicious administration of fluids. If hypotension remains unresponsive to these conservative measures, consider administration of fusopressors (such as phene/phrine) with attention to circulating volume and unine output. As analodipine bes/late tablets is highly protein bound, hemadiallysis is not likely to be of benefit.

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. Amlodipine besylate tablets, USP 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: microarystalline cellulose, can starch, sodium starch glycolate and magnesium stearate.

Experimental data suggest that amlodipine binds to both dihydropyridine and nondihydropyridine

Experimental data suggest minar amalogine binds to both anytoiopyniame and nonaintyroopyniame binding sites. The controller processes of cardiac muscle and wescular smooth muscle are dependent upon the movement of extracellular calcium insis into these cells through specific ion channels. Amologine inhibits calcium ion initize across cell emethymous selectively, with a greater affect on vascular smooth muscle cells than on cardiac muscle cells. Negative inotropic effects can be detected in witho but such effects have not been seen in intoch animals at therapeutic doses. Seam calcium concentration is not affected by moldations. Within the physiologic pH range, amoldpine is an ionized compound (pKe=6.6), and its kinetic interaction with the calcium channel receptor is characterized by a godual 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 amologine relieves angina have not been fully delineated, but are thought to include the following:

Evertional 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 axygen demand, at any given level of exercise.

Vasaspastic Angina: amologiane besylate has been demonstrated to block constriction and restore blood flow in coronary rateries and attricties in response to culcium, patassium epinephrine, serotonin, and thromboarae A2 analogi ne apenimental animal models and in human coronary vessels in vitro. This inhibition of coronary spasm is responsible for the effectiveness of amologiane besylate in vasospastic (Prinzmetal's or variant) angina.

(Instancial softwarming targing).
12.2 Pharmacongrammics: Following administration of threepeutic doses to patients with hypertension, ambidpine basylate produces vocalitation resulting in a reduction of supine and standing bload pressure are not accompanied by a significant change in heart rate or plasma catecholomine levels with chanic dosing. Although the acute introvenous administration of ambidpine decreases are reliabed posteres.

ridine calcium antagonist (calcium ion antagonist or slow-channel blocker) nbrane influx of calcium ions into vascular smooth muscle and cardiac mus

Amlodipine besylate is the besylate salt of amlodipine, a long-acting calcium channel blocker Amlodipine besylate is chemically described as 3Ethyl-5methyl (\pm)-2.[(2-aminoethox)methyl]-4(2-chhorophenyl)-1,4-dihydro-6-methyl-3.5yyridinedicarboxylate, monobenzenesubhonate. Its empirical formula is $2_0H_2S(W_2O_5 \bullet C_0H_2S_2)$, and its structural formula is:

Pediatric Use Amlodipine besylate tablets 2.5 mg to 5 mg daily is effective in lowering blood pressure in patients 6 to 17 years (see *Cinical Studies* (14.1)). Effect of amlodipine besylate tablets on blood pressure in patients less than 6 years of age is not known.

7.14 Drug/Laboratory Test Interactions None known.

²Based on patient weiaht of 50 ka.

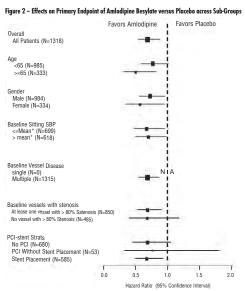
USE IN SPECIFIC POPULATIONS 8.1 Preanancy

Pregnancy Category C

10 OVERDOSAGE

12 CLINICAL PHARMACOLOGY 12.1 Mechanism of Action

- There are no adequate and well-controlled studies in pregnant women. Amlodipine should be used during pregnancy only if the potential benefit justifies the risk to the fetus.
- doing projectively in it me potential events to the rests. In the rests. No evidence of textogenicity or other embryo/fetal toxicity was found when pregnant rats and rabbits wave treated only with annologine moderte at does up to 10 mg annologine/kg/day (respectively, 8 times² and 23 times² the maximum recommended human does of 10 mg on a mg/m² boxis) during their respective particles of major argonapenesis. However, this result interval fractionally determined to the number of intrauterine denths was significantly increased (about 540d) in rats receiving annologine malette at a dose equivalent to 10 mg annologine/kg/day for 14 days before mating and throughout mating and desistion. Annologine moderte has been shown to prolong both the gestation period and the duration of labor in rats at this dose.



*The mean sitting baseline SBP is 129 mmHg.

Table 1 below summarizes the significant composite endpoint and clinical outcomes from the composites of the primary endpoint. The other components of the primary endpoint including cardivascular death, resuscitated cardiac arrest, mycardial infraction, hospitalization for hear failure, stroke/TIA, or peripheral vascular disease did not demonstrate a significant difference between amidolipine besylate and placebo.

Table 1. Incidence of Significant Clinical Outcomes for CAMELOT

Clinical Outcomes	Amlodipine Besylate	Placebo	Risk Reduction
N (%)	(N=663)	(N=655)	(p-value)
Composite CV Endpoint	110	151	31%
	(16.6)	(23.1)	(0.003)
Hospitalization for Angina*	51	84	42%
	(7.7)	(12.8)	(0.002)
Coronary Revascularization*	78	103	27%
	(11.8)	(15.7)	(0.033)

14.5 Studies in Patients with Heart Failure

Studies in Patients with Heart Failure Amologine berylate has been compared to placebo in four 8 to 12 week studies of patients with NYHA Class II/II heart failure based on measures of exarcise tolerance, NYHA classification, symptoms, or left worsneit heart failure based on measures of exarcise tolerance, NYHA classification, symptoms, or left worsneit heart failure based on measures of exarcise tolerance, NYHA classification, symptoms, or left worsneit heart failure based on measures of exarcise tolerance, NYHA classification, symptoms, or left worsneit heart failure based on measures of exarcise tolerance, NYHA classification, symptoms, or left worsneit heart failure based on measures of exarcise tolerance, NYHA classification, and week to inhibitors, andivation of the classification of the combined endpoint of all exase montality modified anythmin, acute myocandial inferction, or hospitalization for worsneit heart failure), or on NYHA despitication, and examples of heart to the primare discuss montality for patients on placebo, for and leaves emotality and cardiac motifiation of the endpoints in the study. Another study (PRAJSE2) randomized patients with NYHA class III (R3N5) on N (PRA) heart failure piacebor, mic caratic motinal events represented adout 2:5× or time enapoints in the study. Another study (PRAISE-2) randomized patients with NYHA Class III (80%) or N (20%) heart failure without dinical symptoms or objective events reduce of anderbying ischemic disease, on stable doese of ACE inhibitors (99%), digitalis (99%), and diuretics (99%), to placebo (n=827) or amladipine besylate (n=827) and followed them for a mean of 33 months. There was no statistically significant difference between annologine besylate and placebo in the primary endpoint of all-access montality (95%); confidence limits from 8% reduction to 29% increase on amlodipine besylate). With amlodipine besylate there were more reports of pulmonary edema.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 2.5 mg Tablets Amlodipine Besylate Tablets USP, equivalent to 2.5 mg of amlodipine are white to aff-white, round, Rest funced, haveled-edge tablets, debassed "C" on one side and "55" on the other side. They are flat-faced, beveled-supplied as follows: NDC 42806-055-09 Bottle of 90 NDC 42806-055-05 Bottle of 500 NDC 42806-055-10 Bottle of 1000

- 16.2 5 mg Tablets Amlodigine Besylate Tablets USP, equivalent to 5 mg of amlodigine are white to aff-white, round, flat-faced, beveled-edge tablets, de-bassed "C56" on one side and plain on the other side. They are supplied as follows: NDC 42806.056.09 Rottle of 90
- NDC 42806-056-05 Bottle of 500 NDC 42806-056-10 Bottle of 1000
- 16.3 10 mg Tablets Amhodipine Besylate Tablets USP, equivalent to 10 mg of amhodipine are white to off-white, round, flar4rcad, bevelot-degla tablets, de-bassed "C57" on one side and plain on the other side. They are supplied as follows:

NDC 42806-057-09 Bottle of 90

- NDC 42806-057-05 Bottle of 500 NDC 42806-057-10 Bottle of 1000
- 16.4 Storage Store bothes at 20° 25°C (68°- 77°F) [See USP Controlled Room Temperature]. Dispense in tight, light-resistant containers (USP). Protect from light.

PATIENT INFORMATION LEAFLET AMLODIPINE BESYLATE TABLETS, USP

Read this information carefully before you start taking **amlodipine besylate tablets** and each time you refill your prescription. There may be new information. This information does not replace talking with your doctor. If you have any questions about amlodipine besylate tablets, ask your doctor. Your doctor will know if amlodipine besylate tablets are right for you.

What are Amlodipine Besylate Tablets?

Amlodipine besylate tablets are a type of medicine known as a calcium channel blocker (CCB). It is used to treat high blood pressure (hypertension) and a type of chest pain called angina. It can be used by itself or with other medicines to treat these conditions.

High Blood Pressure (hypertension)

High blood pressure comes from blood pushing too hard against your blood vessels. Amlodipine besylate tablets relaxes your blood vessels, which lets your blood flow more easily and helps lower your blood pressure. Drugs that lower blood pressure lower your risk of having a stroke or heart attack.

Angina

Angina is a pain or discomfort that keeps coming back when part of your heart does not get enough blood. Angina feels like a pressing or squeezing pain, usually in your chest under the breastbone. Sometimes you can feel it in your shoulders, arms, neck, jaws, or back. Amlodipine besylate tablets can relieve this pain.

Who should not use amlodipine besylate tablets?

Do not use amlodipine besylate tablets if you are allergic to amlodipine (the active ingredient in amlodipine besylate tablets), or to the inactive ingredients. Your doctor or pharmacist can give you a list of these ingredients.

What should I tell my doctor before taking amlodipine besylate tablets?

Tell your doctor about any prescription and non-prescription medicines you are taking, including natural or herbal remedies. Tell your doctor if you:

• ever had heart disease

• ever had liver problems

- are pregnant, or plan to become pregnant. Your doctor will decide if
- amlodipine besylate tablets are the best treatment for you. • are breast-feeding. Do not breast-feed while taking amlodipine besylate tablets. You can stop breast-feeding or take a different medicine

How should I take amlodipine besylate tablets?

- Take amlodipine besylate tablets once a day, with or without food.
- It may be easier to take your dose if you do it at the same time every day, such as with breakfast or dinner, or at bedtime. Do not take more than one dose of **amlodipine besvlate tablets** at a time.

 If you miss a dose, take it as soon as you remember. Do not take amlodipine besylate tablets if it has been more than 12 hours since you missed your last dose. Wait and take the next dose at your regular time.

• Other medicines: You can use nitroglycerin and amlodipine besylate tablets together. If you take nitroglycerin for angina don't stop taking it while you are taking amlodipine besylate tablets

• While you are taking amlodipine besylate tablets, do not stop taking your other prescription medicines, including any other blood

pressure medicines, without talking to your doctor • If you took too much amlodipine besylate tablets, call your doctor or Poison Control Center, or go to the nearest hospital emergency room right away.

What should I avoid while taking amlodipine besylate

- tablets? • Do not breast-feed. It is not known if amlodipine besylate
- tablets will pass through your milk. • Do not start any new prescription or non-prescription medicines or
- supplements, unless you check with your doctor first.

What are the possible side effects of amlodipine besylate tablets?

Amlodipine besylate tablets may cause the following side effects. Most side effects are mild or moderate

swelling	of your	legs or	ankles	
- · · · · · · · · · · · · · · · · · · ·				

- tiredness, extreme sleepiness • stomach pain, nausea
- dizziness
- flushing (hot or warm feeling in your face)
- arrhythmia (irregular heartbeat)
- heart palpitations (very fast heartbeat)

It is rare, but when you first start taking **amlodipine besylate**

tablets or increase your dose, you may have a heart attack or your angina may get worse. If that happens, call your doctor right away or go directly to a hospital emergency room.

Tell your doctor if you are concerned about any side effects you experience. These are not all the possible side effects of amlodipine besylate tablets. For a complete list, ask your doctor or pharmacist.

How do I store amlodipine besylate tablets?

Keep amlodipine besylate tablets away from children. Store amodipine besvlate tablets at room temperature 20° to 25°C (between 68° to 77°F). Keep amlodipine besylate tablets out of the light. Do not store in the bathroom. Keep **amlodipine besylate** tablets in a dry place. Protect from light

General advice about amlodipine besylate tablets Sometimes, doctors will prescribe a medicine for a condition that is not written in the patient information leaflets. Only use amlodipine besylate tablets the way your doctor told you to. Do not give amlodipine besylate tablets to other people, even if they have the

same symptoms you have. It may harm them. You can ask your pharmacist or doctor for information about amlodipine besylate tablets, or you can visit the Epic Pharma

website at www.epic-pharma.com or call 1-888-374-2791.

Manufactured by: Epic Pharma, LLC Laurelton NY 11413 Made in USA

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