1.0 PHARMACOLOGIC CATEGORY
Antihypertensive/Anti-Angina

2.0 DESCRIPTION
Amlodipine besilate (NORVASC®) is the besilate salt of amlodipine, a long-acting calcium channel blocker.

Amlodipine besilate is chemically described as (R.S.) 3-ethyl-5-methyl-2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate benzenesulphonate. Its empirical formula is C\textsubscript{20}H\textsubscript{25}ClN\textsubscript{2}O\textsubscript{5}•C\textsubscript{6}H\textsubscript{6}O\textsubscript{3}S, and its structural formula is:

```
NH
Cl
O
H3C
O
O
CH3
O
H3C
O
NH2
C6H6O3S
```

Amlodipine besilate is a white crystalline powder with a molecular weight of 567.1. It is slightly soluble in water and sparingly soluble in ethanol.

3.0 FORMULATION
Amlodipine besilate (Norvasc) 5 mg: Each tablet contains amlodipine besilate equivalent to 5 mg amlodipine.
Amlodipine besilate (Norvasc) 10 mg: Each tablet contains amlodipine besilate equivalent to 10 mg amlodipine.

4.0 CLINICAL PARTICULARS

4.1 Therapeutic Indications
**Hypertension**

Amlodipine besilate is indicated for the first line of treatment of hypertension and can be used as the sole agent to control blood pressure in the majority of patients. Patients not adequately controlled on a single antihypertensive agent (other than amlodipine) may benefit from the addition of amlodipine, which has been used in combination with a thiazide diuretic, alpha blockers, beta adrenoreceptor blocking agent, or an angiotensin-converting enzyme inhibitor.

Amlodipine besilate is also indicated to reduce the risk of fatal coronary heart disease and non-fatal myocardial infarction, and to reduce the risk of stroke.

**Coronary Artery Disease**

Amlodipine besilate is indicated to reduce the risk of coronary revascularization and the need for hospitalization due to angina in patients with coronary artery disease.

**Chronic Stable Angina**

Amlodipine besilate is indicated for the first line of treatment of myocardial ischemia, whether due to fixed obstruction (stable angina) and/or vasospasm/vasoconstriction (Prinzmetal's or variant angina) of coronary vasculature. Amlodipine besilate may be used where the clinical presentation suggests a possible vasospastic/vasoconstrictive component but where vasospasm/vasoconstriction has not been confirmed. Amlodipine besilate may be used alone, as monotherapy, or in combination with other anti-anginal drugs in patients with angina that is refractory to nitrates and/or adequate doses of beta blockers.

**4.2 Dosage and Method of Administration**

For both hypertension and angina the usual initial dose is 5mg amlodipine once daily which may be increased to a maximum dose of 10mg depending on the individual patient’s response.

For patients with coronary artery disease the recommended dosage range is 5-10 mg once daily. In clinical studies the majority of patients required 10 mg (See section 5.1 Pharmacodynamic Properties - Use in Patients with Coronary Artery Disease (CAD)).

No dose adjustment of amlodipine besilate is required upon concomitant administration of thiazide diuretics, beta-blockers, and angiotensin-converting enzyme inhibitors.

**Use in the Elderly**
Normal dosage regimens are recommended. Amlodipine besilate, used at similar doses in elderly or younger patients, is equally well tolerated.

Use In Children

The recommended 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 section 5.1 Pharmacodynamic Properties and section 5.2 Pharmacokinetic Properties).

The effect of amlodipine on blood pressure in patients less than 6 years of age is not known.

Use in Patients with Impaired Hepatic Function

See section 4.4 Special Warnings and Special Precautions for Use.

Use in Renal Failure

Amlodipine may be used in such patients at normal doses. Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment. Amlodipine is not dialyzable.

4.3 Contraindications

Amlodipine is contraindicated in patients with a known sensitivity to dihydropyridines, amlodipine, including any of the inert component of the tablet.: * Amlodipine is a dihydropyridine calcium channel blocker

4.4 Special Warnings and Special Precautions for Use

Use in Patients with Impaired Hepatic Function

As with all calcium antagonists, amlodipine half-life is prolonged in patients with impaired liver function and dosage recommendations have not been established in these patients. The drug should therefore be administered with caution in these patients.

4.5 Interaction with other medicinal products and other forms of interaction

Amlodipine has been safely administered with thiazide diuretics, alpha blockers, beta blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerine, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.
In vitro data from studies with human plasma indicate that amlodipine has no effect on protein binding of the drugs tested (digoxin, phenytoin, warfarin, or indomethacin).

SIMVASTATIN: Co-administration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily.

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 pharmacokinetics of amlodipine. The study did not allow examination of the effect of genetic polymorphism in CYP3A4, the primary enzyme responsible for metabolism of amlodipine; therefore, administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients resulting in increased blood pressure lowering effects.

In the following studies listed below, there were no significant changes in the pharmacokinetics of either amlodipine or another drug within the study, when co-administered.

Special Studies: Effect of other agents on amlodipine besilate.

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

ALUMINUM/MAGNESIUM (antacid): Co-administration of an aluminum/magnesium antacid with a single dose of amlodipine had no significant effect on the pharmacokinetics of amlodipine.

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

CYP3A4 INHIBITORS: Co-administration of a 180 mg daily dose of diltiazem with 5 mg amlodipine in elderly hypertensive patients (69 to 87 years of age) resulted in a 57% increase in amlodipine systemic exposure. Erythromycin co-administration in healthy volunteers (18 to 43 years of age) did not significantly change amlodipine systemic exposure (22% increase in AUC) Although the clinical relevance of these findings is uncertain, the pharmacokinetic variations may be more pronounced in the elderly. Strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of
amlodipine to a greater extent than diltiazem. Amlodipine should be used with caution together with CYP3A4 inhibitors.

CYP3A4 INDUCERS: There is no data available regarding the effect of CYP3A4 inducers on amlodipine. The concomitant use of CYP3A4 inducers (e.g., rifampicin, hypericum perforatum) may give a lower plasma concentration of amlodipine. Amlodipine should be used with caution together with CYP3A4 inducers.

Special Studies: Effect of amlodipine besilate on other agents.

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

DIGOXIN: Co-administration of amlodipine 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 had no significant effect on the pharmacokinetics of ethanol.

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

CYCLOSPORIN: Pharmacokinetic studies with cyclosporin have demonstrated that amlodipine does not significantly alter the pharmacokinetics of cyclosporin.

Drug/Laboratory Test Interactions: None known.

4.6 Pregnancy and Lactation

Safety of amlodipine in human pregnancy or lactation has not been established. Amlodipine does not demonstrate toxicity in animal reproductive studies other than to delay parturition and prolong labor in rats at a dose level fifty times the maximum recommended dose in humans. Accordingly, use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and fetus.

4.7 Effects on Ability to Drive and Use Machines

Clinical experience with amlodipine indicates that it is unlikely to impair a patient’s ability to drive or use machinery.

4.8 Undesirable Effects
Amlodipine is well tolerated. In placebo controlled clinical trials involving patients with hypertension or angina, the most commonly observed side effects were:

<table>
<thead>
<tr>
<th>MedDRA System Organ Class</th>
<th>Undesirable Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous System Disorders</td>
<td>headache, dizziness, somnolence</td>
</tr>
<tr>
<td>Cardiac Disorders</td>
<td>palpitations</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td>flushing</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>abdominal pain, nausea</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td>edema, fatigue</td>
</tr>
</tbody>
</table>

In these clinical trials no pattern of clinically significant laboratory test abnormalities related to amlodipine has been observed.

Less commonly observed side effects in marketing experience include:

<table>
<thead>
<tr>
<th>MedDRA System Organ Class</th>
<th>Undesirable Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and Lymphatic System Disorders</td>
<td>leukopenia, thrombocytopenia</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td>hyperglycemia</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td>insomnia, mood altered</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>Hypertonia, hypoaesthesia/paresthesia, neuropathy peripheral, syncope, dysgeusia, tremor</td>
</tr>
<tr>
<td>Eye Disorders</td>
<td>visual impairment</td>
</tr>
<tr>
<td>Ear and Labyrinth Disorders</td>
<td>tinnitus</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td>hypotension, vasculitis</td>
</tr>
<tr>
<td>Respiratory, Thoracic, and Mediastinal Disorders</td>
<td>cough, dyspnœa, rhinitis</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>change in bowel habits, dry mouth, dyspepsia (including gastritis), gingival hyperplasia, pancreatitis, vomiting</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td>alopecia, hyperhidrosis, purpura, skin discoloration, urticaria</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td>arthralgia; back pain, muscle spasms, myalgia</td>
</tr>
<tr>
<td>Renal and Urinary Disorders</td>
<td>pollakiuria, micturition disorder, nocturia</td>
</tr>
<tr>
<td>Reproductive System and Breast Disorders</td>
<td>gynecomastia, erectile dysfunction</td>
</tr>
<tr>
<td>General Disorders</td>
<td>asthenia, malaise, pain, weight increased/decreased</td>
</tr>
</tbody>
</table>

Rarely reported events were, allergic reaction including pruritus, rash, angioedema, and erythema multiforme.
Hepatitis, jaundice and hepatic enzyme elevations have also been reported very infrequently (mostly consistent with cholestasis). Some cases severe enough to require hospitalization have been reported in association with use of amlodipine. In many instances, causal association is uncertain.

As with other calcium channel blockers the following adverse events have been rarely reported and cannot be distinguished from the natural history of the underlying disease: myocardial infarction, arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation) and chest pain.

**Pediatric Patients (ages 6-17 years)**

Amlodipine is well tolerated in children. Adverse events were similar to those seen in adults. In a study of 268 children, the most frequently reported adverse events were:

<table>
<thead>
<tr>
<th>MedDRA System Organ Class</th>
<th>Undesirable Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous System Disorders</td>
<td>headaches, dizziness</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td>vasodilatation</td>
</tr>
<tr>
<td>Respiratory, Thoracic, and Mediastinal Disorders</td>
<td>epistaxis</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>abdominal pain</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td>asthenia</td>
</tr>
</tbody>
</table>

The majority of adverse events were mild or moderate. Severe adverse events (predominantly headache) were experienced by 7.2% with amlodipine 2.5mg, 4.5% with amlodipine 5mg, and 4.6% with placebo. The most common cause of discontinuation from the study was uncontrolled hypertension. There were no discontinuations due to laboratory abnormalities. There was no significant change in heart rate.

**4.9 Overdose**

Available data suggest that gross overdosage could result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension, up to and including shock with fatal outcome have been reported.

Administration of activated charcoal to healthy volunteers immediately or up to two hours after ingestion of amlodipine 10 mg has been shown to significantly decrease amlodipine absorption. Gastric lavage may be worthwhile in some cases. Clinically significant hypotension due to amlodipine overdosage calls for active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output. A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of
calcium channel blockade. Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

5.0 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Amlodipine is a calcium ion influx inhibitor (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle.

The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle. The precise mechanism by which amlodipine relieves angina has not been fully determined but amlodipine reduces total ischemic burden by the following two actions.

1) Amlodipine dilates peripheral arterioles and thus, reduces the total peripheral resistance (afterload) against which the heart works. Since the heart rate remains stable, this unloading of the heart reduces myocardial energy consumption and oxygen requirements.

2) The mechanism of action of amlodipine also probably involves dilatation of the main coronary arteries and coronary arterioles, both in normal and ischemic regions. This dilatation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal’s or variant angina) and blunts smoking induced coronary vasoconstriction.

In patients with hypertension, once daily dosing provides clinically significant reductions of blood pressure in both the supine and standing positions throughout the 24 hour interval. Due to the slow onset of action, acute hypotension is not a feature of amlodipine administration.

In patients with angina, once daily administration of amlodipine increases total exercise time, time to angina onset, and time to 1mm ST segment depression, and decreases both angina attack frequency and nitroglycerine tablet consumption.

Amlodipine has not been associated with any adverse metabolic effects or changes in plasma lipids and is suitable for use in patients with asthma, diabetes, and gout.

Use in Patients with Coronary Artery Disease (CAD)

The effects of amlodipine besilate on cardiovascular morbidity and mortality, the progression of coronary atherosclerosis, and carotid atherosclerosis were studied in the Prospective Randomized Evaluation of the Vascular Effects of NORVASC Trial (PREVENT). This multicenter, randomized, double blind, placebo-controlled study followed 825 patients with angiographically defined
coronary artery disease for three years. The population included patients with previous myocardial infarction (MI) (45%), percutaneous transluminal coronary angioplasty (PTCA) at baseline (42%), or history of angina (69%). Severity of CAD ranged from 1-vessel disease (45% of patients) to 3+ vessel disease (21%). Patients with uncontrolled hypertension (DBP > 95 mm Hg) were excluded from the study. Major cardiovascular events were adjudicated by a blinded endpoint committee. Although there were no demonstrable effects on the rate of progression of coronary artery lesions, amlodipine arrested the progression of carotid intima-media thickening. A significant reduction (-31%) was observed in the amlodipine-treated patients in the combined endpoint of cardiovascular death, MI, stroke, PTCA, coronary artery bypass graft (CABG), hospitalization for unstable angina, and worsening congestive heart failure (CHF). A significant reduction (-42%) in revascularization procedures (PTCA and CABG) was also seen in the amlodipine-treated patients. Fewer hospitalizations (-33%) were seen for unstable angina in amlodipine besilate patients than in the placebo group.

The effectiveness of amlodipine besilate in preventing clinical events in patients with coronary artery disease (CAD) has been evaluated in an independent, multicenter, randomized, double-blind, placebo-controlled study of 1997 patients; Comparison of Amlodipine vs. Enalapril to Limit Occurrences of Thrombosis (CAMELOT)\textsuperscript{15}. Of these patients, 663 were treated with amlodipine 5-10 mg and 655 patients were treated with placebo, in addition to standard care of statins, beta-blockers, diuretics and aspirin, for 2 years. The key efficacy results are presented in Table 1. The results indicate that amlodipine treatment was associated with fewer hospitalizations for angina and revascularization procedures in patients with CAD.

### Table 1. Incidence of Significant Clinical Outcomes for CAMELOT

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

* 1). Defined in CAMELOT as cardiovascular death, nonfatal MI, resuscitated cardiac arrest, coronary revascularization, hospitalization for angina pectoris, hospitalization for congestive heart failure, fatal or nonfatal stroke or TIA, any diagnosis of PVD in a subject not previously diagnosed as having PVD or any admission for a procedure for the treatment of PVD
2). The composite CV endpoint was the primary efficacy endpoint in CAMELOT.

*Treatment to Prevent Heart Attack Trial (ALLHAT)*

A randomized double-blind morbidity-mortality study called the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was performed to compare newer drug therapies: amlodipine 2.5-10 mg/d (calcium channel blocker) or lisinopril 10-40 mg/d (ACE-inhibitor) as first-line therapies to that of the thiazide-diuretic, chlorthalidone 12.5-25 mg/d in mild to moderate hypertension.

A total of 33,357 hypertensive patients aged 55 or older were randomized and followed for a mean of 4.9 years. The patients had at least one additional CHD risk factor, including myocardial infarction or stroke > 6 months or documentation of other atherosclerotic CVD (overall 51.5%), type 2 diabetes (36.1%), HDL-C < 35 mg/dL (11.6%), left ventricular hypertrophy diagnosed by electrocardiogram or echocardiography (20.9%), current cigarette smoking (21.9%).

The primary endpoint was a composite of fatal CHD or non-fatal myocardial infarction. There was no significant difference in the primary endpoint between amlodipine-based therapy and chlorthalidone-based therapy: RR 0.98 95% CI [0.90-1.07] p=0.65. In addition, there was no significant difference in all-cause mortality between amlodipine-based therapy and chlorthalidone-based therapy: RR 0.96 95% CI [0.89-1.02] p=0.20.

*Use in Patients with Heart Failure*

Hemodynamic studies and exercise based controlled clinical trials in NYHA Class II-IV heart failure patients have shown that amlodipine did not lead to clinical deterioration as measured by exercise tolerance, left ventricular ejection fraction and clinical symptomatology.

A placebo controlled study (PRAISE) designed to evaluate patients in NYHA Class III-IV heart failure receiving digoxin, diuretics and angiotensin-converting enzyme (ACE) inhibitors has shown that amlodipine did not lead to an increase in risk of mortality or combined mortality and morbidity in patients with heart failure.

In a follow-up, long-term, placebo controlled study (PRAISE-2) of amlodipine in patients with NYHA III and IV heart failure without clinical symptoms or objective findings suggestive of underlying ischemic disease, on stable doses of ACE inhibitors, digitalis, and diuretics, amlodipine had no effect on total or cardiovascular mortality. In this same population amlodipine was associated with increased reports of pulmonary edema despite no significant difference in the incidence of worsening heart failure as compared to placebo.

*Use in Pediatric Patients  (Ages 6 to 17 years)*
The efficacy of amlodipine besilate in hypertensive pediatric patients 6 to 17 years of age was demonstrated in one 8-week double-blind, placebo-controlled randomized withdrawal trial in 268 patients with hypertension. All patients were randomized to the 2.5mg or 5mg treatment arms and followed for 4 weeks after which they were randomized to continue 2.5mg or 5mg amlodipine or placebo for an additional 4 weeks. Compared with baseline, once daily treatment with amlodipine 5mg resulted in statistically significant reductions in systolic and diastolic blood pressures. Placebo-adjusted, mean reduction in seated systolic blood pressure was estimated to be 5.0 mmHg for the 5 mg dose of amlodipine and 3.3 mmHg for the 2.5 mg dose of amlodipine. Subgroup analyses indicated that younger pediatric patients aged 6 to 13 years had efficacy results comparable to those of the older pediatric patients aged 14 to 17 years.

5.2 Pharmacokinetic Properties

Absorption

After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours postdose. Absolute bioavailability has been estimated to be between 64 and 80%. The volume of distribution is approximately 21 L/kg. In vitro studies have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins.

Absorption of amlodipine is unaffected by consumption of food.

Biotransformation/Elimination

The terminal plasma elimination half life is about 35-50 hours and is consistent with once daily dosing. Steady state plasma levels are reached after 7-8 days of consecutive dosing. Amlodipine is extensively metabolized by the liver to inactive metabolites with 10% of the parent compound and 60% of metabolites excreted in the urine.

Use in the Elderly

The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. Amlodipine clearance tends to be decreased with resulting increases in AUC and elimination half-life in elderly patients. Increases in AUC and elimination half life in patients with congestive heart failure were as expected for the patient age group studied.

Use in Pediatrics

In one clinical chronic exposure study, 73 hypertensive pediatric patients, ages 12 months to less than or equal to 17 years, amlodipine was dosed at an average daily dose of 0.17 mg/kg. Clearance for subjects with the median weight of 45 kg were 23.7 l/hr and 17.6 l/hr for males and females, respectively. This is in a similar range to the published estimates of 24.8 l/hr in a 70 kg adult. The average estimate for volume of distribution for a 45 kg patient was 1130 L (25.11 l/kg). Maintenance of the blood pressure effect over the 24-hour dosing
interval was observed with little difference in peak and trough variation effect. When compared with historical adult pharmacokinetics the parameters observed in this study indicate that once daily dosing is appropriate.

### 5.3 Preclinical Safety Data

_Carcinogenesis, Mutagenesis, Impairment of Fertility_ - Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m² basis) was close to the maximum tolerated dose for mice but not for rats.

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

There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg on a mg/m² basis).

*Based on patient weight of 50 kg.

### 6.0 Pharmaceutical Particulars

#### 6.1 Shelf-Life
See expiry date on outer package

#### 6.2 Storage
Store at room temperature not exceeding 30 °C.

#### 6.3 Availability:

Amlodipine besilate (Norvasc) 5 mg are white, emerald shaped tablets imprinted with NVC/5 on one side and Pfizer on the other side. Available as blisterpack of 10’s in boxes of 100’s.

Amlodipine besilate (Norvasc) 10 mg are white, emerald shaped tablets imprinted with NVC/10 on one side and Pfizer on the other side. Available as blisterpack of 10’s in boxes of 100’s.

Amlodipine besilate (Norvasc) 5 mg are white, emerald shaped tablets imprinted with NVC/5 on one side and Pfizer on the other side. Available as blisterpack of 10’s in boxes of 100’s or 500’s for hospital use only.

Amlodipine besilate (Norvasc) 10 mg are white, emerald shaped tablets imprinted with NVC/10 on one side and Pfizer on the other side. Available as blisterpack of 10’s in boxes of 100’s or 500’s for hospital use only.
References


8. Data on File: Amlodipine International Registration Dossier Volumes 1 - 6


38. Study report: Protocol 053-369, Darnis F and Poupon R. An open study to assess the safety and pharmacokinetic profile of oral amlodipine in patients with stable chronic hepatic insufficiency compared with a group of convalescing subjects without hepatic impairment. (Pfizer, Inc. data)


45.