ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

Note: This SPC, labelling and packages leaflet is the version valid at the time of Commission decision.

After the Commission decision the Member State competent authorities, in liaison with the reference Member State, will update the product information as required. Therefore, this SPC, labelling and package leaflet may not necessarily represent the current text.

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Norvasc and associated names (see Annex I) 5 mg tablets
Norvasc and associated names (see Annex I) 10 mg tablets
Norvasc and associated names (see Annex I) 5 mg hard capsules
Norvasc and associated names (see Annex I) 10 mg hard capsules

[See Annex I - to be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains amlodipine besilate equivalent to 5 mg amlodipine.
Each tablet contains amlodipine besilate equivalent to 10 mg amlodipine.
Each hard capsule contains amlodipine besilate equivalent to 5 mg amlodipine.
Each hard capsule contains amlodipine besilate equivalent to 10 mg amlodipine.

Excipients:
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.
5 mg tablets: White to off-white, emerald-shaped tablets engraved AML 5 and breaker score on one side and Pfizer logo on the other side.
10 mg tablets: White to off-white, emerald-shaped tablets engraved AML-10 on one side and Pfizer logo on the other side.

5 mg tablets: White to off-white, emerald-shaped tablets engraved AML 5 and breaker score on one side and blank on the other side.
10 mg tablets: White to off-white, emerald-shaped tablets engraved AML-10 on one side and blank on the other side.

Hard capsule.
5 mg hard capsules: Yellow and white capsules with black imprint AML 5 on one side and Pfizer logo on the other.
10 mg hard capsules: Grey capsules with black imprint AML 10 on one side and Pfizer logo on the other.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertension
Chronic stable angina pectoris
Vasospastic (Prinzmetal's) angina

4.2 Posology and method of administration

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

In hypertensive patients, Norvasc has been used in combination with a thiazide diuretic, alpha blocker, beta blocker, or an angiotensin converting enzyme inhibitor. For angina, Norvasc may be used as monotherapy or in combination with other antianginal medicinal products in patients with angina that is refractory to nitrates and/or to adequate doses of beta blockers.

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

Special populations

Elderly
Norvasc used at similar doses in elderly or younger patients is equally well tolerated. Normal dosage regimens are recommended in the elderly, but increase of the dosage should take place with care (see sections 4.4 and 5.2).

Hepatic impairment
Dosage recommendations have not been established in patients with mild to moderate hepatic impairment; therefore dose selection should be cautious and should start at the lower end of the dosing range (see sections 4.4 and 5.2). The pharmacokinetics of amlodipine have not been studied in severe hepatic impairment. Amlodipine should be initiated at the lowest dose and titrated slowly in patients with severe hepatic impairment.

Renal impairment
Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment, therefore the normal dosage is recommended. Amlodipine is not dialysable.

Paediatric population
Children and adolescents with hypertension from 6 years to 17 years of age
The recommended antihypertensive oral dose in paediatric patients ages 6-17 years is 2.5 mg once daily as a starting dose, up-titrated to 5 mg once daily if blood pressure goal is not achieved after 4 weeks. Doses in excess of 5 mg daily have not been studied in paediatric patients (see sections 5.1 and 5.2).

Doses of amlodipine 2.5 mg are not possible with this medicinal product.

Children under 6 years old
No data are available.

Method of administration
Tablet for oral administration.
Hard capsule for oral administration.

4.3 Contraindications

Amlodipine is contraindicated in patients with:

hypersensitivity to dihydropyridine derivatives, amlodipine or to any of the excipients.
severe hypotension.
shock (including cardiogenic shock).
obstruction of the outflow tract of the left ventricle (e.g., high grade aortic stenosis).
haemodynamically unstable heart failure after acute myocardial infarction.

4.4 Special warnings and precautions for use

The safety and efficacy of amlodipine in hypertensive crisis has not been established.

Patients with cardiac failure
Patients with heart failure should be treated with caution. In a long-term, placebo controlled study in patients with severe heart failure (NYHA class III and IV) the reported incidence of pulmonary oedema was higher in the amlodipine treated group than in the placebo group (see section 5.1). Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.

Use in patients with impaired hepatic function
The half life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function; dosage recommendations have not been established. Amlodipine should therefore be initiated at the lower end of the dosing range and caution should be used, both on initial treatment and when increasing the dose. Slow dose titration and careful monitoring may be required in patients with severe hepatic impairment.

Use in elderly patients
In the elderly increase of the dosage should take place with care (see sections 4.2 and 5.2).

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 dialysable.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on amlodipine
CYP3A4 inhibitors: Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to significant increase in amlodipine exposure. The clinical translation of these PK variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be required.

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.

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.

Dantrolene (infusion): In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalemia, it is recommended that the co-administration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

Effects of amlodipine on other medicinal products
The blood pressure lowering effects of amlodipine adds to the blood pressure-lowering effects of other medicinal products with antihypertensive properties.

In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin, warfarin or cyclosporin.

4.6 Fertility, pregnancy and lactation

Pregnancy
The safety of amlodipine in human pregnancy has not been established.

In animal studies, reproductive toxicity was observed at high doses (see section 5.3).

Use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and foetus.

Breast-feeding
It is not known whether amlodipine is excreted in breast milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with amlodipine should be made taking into account the benefit of breast-feeding to the child and the benefit of amlodipine therapy to the mother.

Fertility
Reversible biochemical changes in the head of spermatozoa have been reported in some patients treated by calcium channel blockers. Clinical data are insufficient regarding the potential effect of amlodipine on fertility. In one rat study, adverse effects were found on male fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Amlodipine can have minor or moderate influence on the ability to drive and use machines. If patients taking amlodipine suffer from dizziness, headache, fatigue or nausea the ability to react may be impaired. Caution is recommended especially at the start of treatment.

4.8 Undesirable effects

Summary of the safety profile
The most commonly reported adverse reactions during treatment are somnolence, dizziness, headache, palpitations, flushing, abdominal pain, nausea, ankle swelling, oedema and fatigue.

Tabulated list of adverse reactions
The following adverse reactions have been observed and reported during treatment with amlodipine with the following frequencies: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to ≤1/100); rare (≥1/10,000 to ≤1/1,000); very rare (≤1/10,000).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System organ class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Very rare	Leukocytopenia, thrombocytopenia
Immune system disorders	Very rare	Allergic reactions
Metabolism and nutrition disorders	Very rare	Hyperglycaemia
Psychiatric disorders	Uncommon	Insomnia, mood changes (including anxiety), depression
	Rare	Confusion
Nervous system disorders	Common	Somnolence, dizziness, headache (especially at the beginning of the treatment)
	Uncommon	Tremor, dysgeusia, syncope, hypoesthesia, paresthesia
	Very rare	Hypertonia, peripheral neuropathy
Eye disorders	Uncommon	Visual disturbance (including diplopia)

Ear and labyrinth disorders	Uncommon	Tinnitus
Cardiac disorders	Common	Palpitations
	Very rare	Myocardial infarction, arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)
Vascular disorders	Common	Flushing
	Uncommon	Hypotension
	Very rare	Vasculitis
Respiratory, thoracic and mediastinal disorders	Uncommon	Dyspnoea, rhinitis
	Very rare	Cough
Gastrointestinal disorders	Common	Abdominal pain, nausea
	Uncommon	Vomiting, dyspepsia, altered bowel habits (including diarrohea and constipation), dry mouth
	Very rare	Pancreatitis, gastritis, gingival hyperplasia
Hepatobiliary disorders	Very rare	Hepatitis, jaundice, hepatic enzymes increased*
Skin and subcutaneous tissue disorders	Uncommon	Alopecia, purpura, skin discolouration, hyperhidrosis, pruritus, rash, exanthema
	Very rare	Angioedema, erythema multiforme, urticaria, exfoliative dermatitis, Stevens-Johnson syndrome, Quincke oedema, photosensitivity
Musculoskeletal and connective tissue disorders	Common	Ankle swelling
	Uncommon	Arthralgia, myalgia, muscle cramps, back pain
Renal and urinary disorders	Uncommon	Micturition disorder, nocturia, increased urinary frequency
Reproductive system and breast disorders	Uncommon	Impotence, gynecomastia
General disorders and administration site conditions	Common	Oedema, fatigue
	Uncommon	Chest pain, asthenia, pain, malaise
Investigations	Uncommon	Weight increase, weight decrease

*mostly consistent with cholestasis

Exceptional cases of extrapyramidal syndrome have been reported.

4.9 Overdose

In humans experience with intentional overdose is limited.

Symptoms
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.

Treatment
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.

Gastric lavage may be worthwhile in some cases. In healthy volunteers the use of charcoal up to 2 hours after administration of amlodipine 10 mg has been shown to reduce the absorption rate of amlodipine.

Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Calcium channel blockers, selective calcium channel blockers with mainly vascular effects. ATC Code: C08CA01.
Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group (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 ischaemic 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 ischaemic regions. This dilatation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal's or variant angina).

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 glyceryl trinitrate 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 effectiveness of amlodipine in preventing clinical events in patients with coronary artery disease (CAD) has been evaluated in an independent, multi-center, randomized, double- blind, placebo-controlled study of 1997 patients; Comparison of Amlodipine vs. Enalapril to Limit Occurrences of Thrombosis (CAMELOT). Of these patients, 663 were treated with amlodipine 5-10 mg, 673 patients were treated with enalapril 10-20 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

	Cardiovascular event rates, No. (%)			Amlodipine vs. Placebo	
Outcomes	Amlopidine	Placebo	Enalapril	Hazard Ratio (95% CI)	*P* Value
Primary Endpoint					
Adverse cardiovascular events	110 (16.6)	151 (23.1)	136 (20.2)	0.69 (0.54-0.88)	.003
Individual Components					
Coronary revascularization	78 (11.8)	103 (15.7)	95 (14.1)	0.73 (0.54-0.98)	.03
Hospitalization for angina	51 (7.7)	84 (12.8)	86 (12.8)	0.58 (0.41-0.82)	.002
Nonfatal MI	14 (2.1)	19 (2.9)	11 (1.6)	0.73 (0.37-1.46)	.37
Stroke or TIA	6 (0.9)	12 (1.8)	8 (1.2)	0.50 (0.19-1.32)	.15
Cardiovascular death	5 (0.8)	2 (0.3)	5 (0.7)	2.46 (0.48-12.7)	.27
Hospitalization for CHF	3 (0.5)	5 (0.8)	4 (0.6)	0.59 (0.14-2.47)	.46
Resuscitated cardiac arrest	0	4 (0.6)	1 (0.1)	NA	.04
New-onset peripheral vascular disease	5 (0.8)	2 (0.3)	8 (1.2)	2.6 (0.50-13.4)	.24

Abbreviations: CHF, congestive heart failure; CI, confidence interval; MI, myocardial infarction; TIA, transient ischemic attack.
Use in patients with heart failure
Haemodynamic studies and exercise based controlled clinical trials in NYHA Class II-IV heart failure patients have shown that Norvasc did not lead to clinical deterioration as measured by exercise tolerance, left ventricular ejection fraction and clinical symptomatology.

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

In a follow-up, long term, placebo controlled study (PRAISE-2) of Norvasc in patients with NYHA III and IV heart failure without clinical symptoms or objective findings suggestive or underlying ischaemic disease, on stable doses of ACE inhibitors, digitalis, and diuretics, Norvasc had no effect on total cardiovascular mortality. In this same population Norvasc was associated with increased reports of pulmonary oedema.

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: previous myocardial infarction or stroke (> 6 months prior to enrollment) 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. Among secondary endpoints, the incidence of heart failure (component of a composite combined cardiovascular endpoint) was significantly higher in the amlodipine group as compared to the chlorthalidone group (10.2% vs. 7.7%, RR 1.38, 95% CI [1.25-1.52] p<0.001). However, 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 children (aged 6 years and older)
In a study involving 268 children aged 6-17 years with predominantly secondary hypertension, comparison of a 2.5mg dose, and 5.0 mg dose of amlodipine with placebo, showed that both doses reduced Systolic Blood Pressure significantly more than placebo. The difference between the two doses was not statistically significant.

The long-term effects of amlodipine on growth, puberty and general development have not been studied. The long-term efficacy of amlodipine on therapy in childhood to reduce cardiovascular morbidity and mortality in adulthood have also not been established.

5.2 Pharmacokinetic properties

Absorption, distribution, plasma protein binding: After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours post dose. 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.

The bioavailability of amlodipine is not affected by food intake.

Biotransformation/elimination
The terminal plasma elimination half life is about 35-50 hours and is consistent with once daily dosing. Amlodipine is extensively metabolised by the liver to inactive metabolites with 10% of the parent compound and 60% of metabolites excreted in the urine.

Use in hepatic impairment
Very limited clinical data are available regarding amlodipine administration in patients with hepatic impairment. Patients with hepatic insufficiency have decreased clearance of amlodipine resulting in a longer half-life and an increase in AUC of approximately 40-60%.

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 children
A population PK study has been conducted in 74 hypertensive children aged from 1 to 17 years (with 34 patients aged 6 to 12 years and 28 patients aged 13 to 17 years) receiving amlodipine between 1.25 and 20 mg given either once or twice daily. In children 6 to 12 years and in adolescents

5.3 Preclinical safety data

Reproductive toxicology
Reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labour and decreased pup survival at dosages approximately 50 times greater than the maximum recommended dosage for humans based on mg/kg.

Impairment of fertility
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). In another rat study in which male rats were treated with amlodipine besilate for 30 days at a dose comparable with the human dose based on mg/kg, decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells.

Carcinogenesis, mutagenesis
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.

*Based on patient weight of 50 kg

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

5 mg and 10 mg tablets
Microcrystalline cellulose,
dibasic calcium phosphate anhydrous,
sodium starch glycolate,
magnesium stearate.

5 mg and 10 mg hard capsules
Hard capsule content:
Microcrystalline cellulose,
maize starch,
magnesium stearate.

Hard capsule shell
5 mg:
Gelatin,
quinoline yellow,
black iron oxide,

titanium dioxide.

10 mg:
Gelatin,
black iron oxide,
yellow iron oxide,
titanium dioxide.

Printing ink
Shellac glaze,
black iron oxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 mg and 10 mg tablets

4 years

5 mg and 10 mg hard capsules

5 years

6.4 Special precautions for storage

5 mg and 10 mg tablets

Do not store above 25°C

5 mg and 10 mg hard capsules

Do not store above 30°C.

6.5 Nature and contents of container

5 mg tablets
PVC-PVDC/Al blisters containing 4, 10, 14, 20, 28, 30, 50, 60, 98, 100, 300, 500 tablets
PVC-PVDC/Al blisters in calendar packs containing 28 and 98 tablets
PVC-PVDC/Al unit dose blisters containing 50x1 and 500x1 tablets

10 mg tablets
PVC-PVDC/Al blisters containing 4, 10, 14, 20, 28, 30, 50, 60, 90, 98, 100, 300, 500 tablets
PVC-PVDC/Al blisters in calendar packs containing 28 and 98 tablets
PVC-PVDC/Al unit dose blisters containing 50x1 and 500x1 tablets

5 mg hard capsules
PVC-PVDC/Al blisters containing 14, 28, 30, 56, 90, 98 and 100 capsules
PVC-PVDC/Al unit dose blisters containing 28x1, 56x1 and 100x1 capsules

10 mg hard capsules
PVC-PVDC/Al blisters containing 14, 28, 30, 56, 90, 98 and 100 capsules
PVC-PVDC/Al unit dose blisters containing 30x1, 56x1 and 100x1 capsules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<{DD/MM/YYYY}> <{DD month YYYY}>

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

<{MM/YYYY}>

[To be completed nationally]

Detailed information on this medicinal product is available on the website of {name of MS/Agency}

[To be completed nationally]

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Norvasc and associated names 5 mg tablets
Norvasc and associated names 10 mg tablets
Norvasc and associated names 5 mg hard capsules
Norvasc and associated names 10 mg hard capsules

[See Annex I - To be completed nationally]

Amlodipine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains amlodipine besilate equivalent to 5 mg amlodipine
Each tablet contains amlodipine besilate equivalent to 10 mg amlodipine
Each hard capsule contains amlodipine besilate equivalent to 5 mg amlodipine
Each hard capsule contains amlodipine besilate equivalent to 10 mg amlodipine

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

5 mg tablet
4 tablets
10 tablets
14 tablets
20 tablets
28 tablets
30 tablets
50 tablets
50x1 tablets
60 tablets
98 tablets
100 tablets
300 tablets
500 tablets
500x1 tablets

10 mg tablet
4 tablets
10 tablets
14 tablets
20 tablets

28 tablets
30 tablets
50 tablets
50x1 tablets
60 tablets
90 tablets
98 tablets
100 tablets
300 tablets
500 tablets
500x1 tablets

5 mg hard capsule
14 capsules
28 capsules
28x1 capsules
30 capsules
56 capsules
56x1 capsules
90 capsules
98 capsules
100 capsules
100x1 capsules

10 mg hard capsule
14 capsules
28 capsules
30 capsules
30x1 capsules
56 capsules
56x1 capsules
90 capsules
98 capsules
100 capsules
100x1 capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Tablets: Do not store above 25°C

Hard Capsules: Do not store above 30°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

[See Annex I - To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[To be completed nationally]

MINIMUM PARTICULARS TO APPEAR ON BLISTERS

BLISTERS

- **plain and unit dose packs (tablets and capsules)**
- **plain calendar packs (tablets only)**

1. NAME OF THE MEDICINAL PRODUCT

Norvasc and associated names 5 mg tablets
Norvasc and associated names 10 mg tablets
Norvasc and associated names 5 mg hard capsules
Norvasc and associated names 10 mg hard capsules

[See Annex I - To be completed nationally]

Amlodipine
Tablet
Hard capsule

2. NAME OF THE MARKETING AUTHORISATION HOLDER

{Name}

[See Annex I - To be completed nationally]

3. EXPIRY DATE

Exp

4. BATCH NUMBER

Lot

5. OTHER

{For plain blisters of 7 tablets – the abbreviated days of the week may be printed on the foil for each tablet i.e., MON, TUE, WED, THU, FRI, SAT, SUN}

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Norvasc and associated names (see Annex I) 5 mg and 10 mg tablets
Norvasc and associated names (see Annex I) 5 mg and 10 mg hard capsules
[See Annex I - to be completed nationally]

Amlodipine

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again
- If you have any further questions, ask your doctor or pharmacist
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist

In this leaflet:

1. WHAT NORVASC IS AND WHAT IT IS USED FOR

Norvasc contains the active substance amlodipine which belongs to a group of medicines called calcium antagonists.

Norvasc is used to treat high blood pressure (hypertension) or a certain type of chest pain called angina, a rare form of which is Prinzmetal's or variant angina.

In patients with high blood pressure your medicine works by relaxing blood vessels, so that blood passes through them more easily. In patients with angina Norvasc works by improving blood supply to the heart muscle which then receives more oxygen and as a result chest pain is prevented. Your medicine does not provide immediate relief of chest pain from angina.

2. BEFORE YOU TAKE NORVASC

Do not take Norvasc

- If you are allergic (hypersensitive) to amlodipine, or any of the other ingredients of your medicine listed in section 6, or to any other calcium antagonists. This may be itching, reddening of the skin or difficulty in breathing.
- If you have severe low blood pressure (hypotension)
- If you have narrowing of the aortic heart valve (aortic stenosis) or cardiogenic shock (a condition where your heart is unable to supply enough blood to the body).
- If you suffer from heart failure after a heart attack

Take special care with Norvasc

You should inform your doctor if you have or have had any of the following conditions:

- Recent heart attack
- Heart failure
- Severe increase in blood pressure (Hypertensive crisis)
- Liver disease
- You are elderly and your dose needs to be increased

Use in children and adolescents
Norvasc has not been studied in children under the age of 6 years. Norvasc should only used for hypertension in children and adolescents from 6 years to 17 years of age (see section 3).
For more information, talk to your doctor.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription**.**

Norvasc may affect or be affected by other medicines, such as:
- ketoconazole, itraconazole (anti-fungal medicines)
- ritonavir, indinavir, nelfinavir (so called protease inhibitors used to treat HIV)
- rifampicin, erythromycin, clarithromycin (antibiotics)
- hypericum perforatum (St. John's Wort)
- verapamil, diltiazem (heart medicines)
- dantrolene (infusion for severe body temperature abnormalities)

Norvasc may lower your blood pressure even more if you are already taking other medicines to treat your high blood pressure.

Taking Norvasc with food and drink
Grapefruit juice and grapefruit should not be consumed by people who are taking Norvasc. This is because grapefruit and grapefruit juice can lead to an increase in the blood levels of the active ingredient amlodipine, which can cause an unpredictable increase in the blood pressure lowering effect of Norvasc.

Pregnancy
The safety of amlodipine in human pregnancy has not been established. If you think you might be pregnant, or are planning to get pregnant, you must tell your doctor before you take Norvasc.

Breast-feeding
It is not known whether amlodipine is passed into breast milk. If you are breast-feeding or about to start breast-feeding you must tell your doctor before taking Norvasc.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
Norvasc may affect your ability to drive or use machines. If the tablets capsules make you feel sick, dizzy or tired, or give you a headache, do not drive or use machines and contact your doctor immediately.

Important information about some of the ingredients of Norvasc
This medicine contains less than 1 mmol sodium (23 mg) per tablet capsule, which means is essentially 'sodium-free'.

3. HOW TO TAKE NORVASC

Always take your medicine exactly as your doctor has told you. You should check with your doctor or phamacist if you are not sure.

The usual initial dose is Norvasc 5 mg once daily. The dose can be increased to Norvasc 10 mg once daily.

Your medicine can be used before or after food and drinks. You should take your medicine at the same time each day with a drink of water. Do not take Norvasc with grapefruit juice.

Use in children and adolescents
For children and adolescents (6-17 years old), the recommended usual starting dose is 2.5 mg a day. The maximum recommended dose is 5 mg a day. Amlodipine 2.5 mg is not currently available and the 2.5 mg dose cannot be obtained with Norvasc 5 mg tablets as these tablets are not manufactured to break into two equal halves.

For children and adolescents (6-17 years old), the recommended usual starting dose is 2.5 mg a day. The maximum recommended dose is 5 mg a day. Norvasc capsules 2.5 mg are currently not available.

It is important to keep taking the tablets capsules. Do not wait until your tablets capsules are finished before seeing your doctor.

If you take more Norvasc than you should
Taking too many tablets may cause your blood pressure to become low or even dangerously low. You may feel dizzy, lightheaded, faint or weak. If blood pressure drop is severe enough shock can occur. Your skin could feel cool and clammy and you could lose consciousness. Seek immediate medical attention if you take too many Norvasc tablets.

If you forget to take Norvasc
Do not worry. If you forget to take a tablet capsule, leave out that dose completely. Take your next dose at the right time. Do not take a double dose to make up for a missed dose.

If you stop taking Norvasc
Your doctor will advise you how long to take your medicine. Your condition may return if you stop using your medicine before you are advised.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Norvasc can cause side effects, although not everybody gets them.

Visit your doctor **immediately** if you experience any of the following very rare, severe side effects after taking this medicine.

- Sudden wheeziness, chest pain, shortness of breath or difficulty in breathing
- Swelling of eyelids, face or lips
- *Swelling of the tongue and throat which causes great difficulty breathing*
- *Severe skin reactions including intense skin rash, hives, reddening of the skin over your whole body, severe itching, blistering, peeling and swelling of the skin, inflammation of mucous membranes (Stevens Johnson Syndrome) or other allergic reactions*
- Heart attack, abnormal heart beat
- *Inflamed pancreas which may cause severe abdominal and back pain accompanied with feeling very unwell*

The following **common side-effects** have been reported. If any of these cause you problems or if they **last for more than one week**, you should **contact your doctor.**

Common: affects 1 to 10 users in 100
- Headache, dizziness, sleepiness (especially at the beginning of treatment)
- Palpitations (awareness of your heart beat), flushing
- Abdominal pain, feeling sick (nausea)
- Ankle swelling (oedema), tiredness

Other side-effects that have been reported include the following list. If any of these get serious, or if you notice any side-effects not listed in this leaflet, please tell your doctor or pharmacist.

Uncommon: affects 1 to 10 users in 1,000

- Mood changes, anxiety, depression, sleeplessness
- Trembling, taste abnormalities, fainting, weakness
- Numbness or tingling sensation in your limbs; loss of pain sensation
- Visual disturbances, double vision, ringing in the ears
- Low blood pressure
- Sneezing/running nose caused by inflammation of the lining of the nose (rhinitis)
- Altered bowel habits, diarrhoea, constipation, indigestion, dry mouth, vomiting (being sick)
- Hair loss, increased sweating, itchy skin, red patches on skin, skin discolouration
- Disorder in passing urine, increased need to urinate at night, increased number of times of passing urine
- Inability to obtain an erection; discomfort or enlargement of the breasts in men
- Weakness, pain, feeling unwell
- Joint or muscle pain, muscle cramps, back pain
- Weight increase or decrease

Rare: affects 1 to 10 users in 10,000

- Confusion

Very rare: affects less than 1 user in 10,000

- Decreased numbers of white blood cells, decrease in blood platelets which may result in unusual bruising or easy bleeding (red blood cell damage)
- Excess sugar in blood (hyperglycaemia)
- A disorder of the nerves which can cause weakness, tingling or numbness
- Cough, swelling of the gums
- Abdominal bloating (gastritis)
- Abnormal liver function, inflammation of the liver (hepatitis), yellowing of the skin (jaundice), liver enzyme increase which may have an effect on some medical tests
- Increased muscle tension
- Inflammation of blood vessels, often with skin rash
- Sensitivity to light
- Disorders combining rigidity, tremor, and/or movement disorders

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE NORVASC

Keep out of the reach and sight of children.

Do not use your medicine after the expiry date which is stated on the pack after 'EXP'. The expiry date refers to the last day of that month.

Tablets
Do not store above 25^{o}C.

Capsules
Do not store above 30^{o}C.

Medicines should not be disposed of via wastewater of household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Norvasc contains
The active substance in Norvasc 5 mg tablets is amlodipine (as besilate).
The active substance in Norvasc 10 mg tablets is amlodipine (as besilate).
The other ingredients are dibasic calcium phosphate, magnesium stearate, microcrystalline cellulose and sodium starch glycolate.

The active substance in Norvasc 5 mg capsules is amlodipine (as besilate).
The active substance in Norvasc 10 mg capsules is amlodipine (as besilate).
The other ingredients are microcrystalline cellulose, maize starch, magnesium stearate.
The capsule shell contains:
- 5 mg: gelatin, quinoline yellow, black iron oxide, titanium dioxide.
- 10 mg: gelatin, black iron oxide, yellow iron oxide, titanium dioxide.
The capsule shell printing inks contain: Shellac glaze, black iron oxide.

What Norvasc looks like and contents of the pack

5 mg tablets: White to off-white, emerald-shaped tablets engraved AML 5 and breaker score on one side and Pfizer logo on the other side.
10 mg tablets: White to off-white, emerald-shaped tablets engraved AML-10 on one side and Pfizer logo on the other side.

5 mg tablets: White to off-white, emerald-shaped tablets engraved AML 5 and breaker score on one side and blank on the other side.
10 mg tablets: White to off-white, emerald-shaped tablets engraved AML-10 on one side and blank on the other side.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

Norvasc 5 mg tablets are available in blister packs containing 4, 10, 14, 20, 28, 30, 50, 60, 98, 100, 300, 500 tablets and in unit dose blister packs containing 50x1 and 500x1 tablets.

Norvasc 10 mg tablets are available in blister packs containing 4, 10, 14, 20, 28, 30, 50, 60, 90, 98, 100, 300, 500 tablets and in unit dose blister packs containing 50x1 and 500x1 tablets.

5 mg hard capsules: Yellow and white capsules with black imprint AML 5 on one side and Pfizer logo on the other.
10 mg hard capsules: Grey capsules with black imprint AML 10 on one side and Pfizer logo on the other.

Norvasc 5 mg capsules are available in blister packs containing 14, 28, 30, 56, 90, 98 and 100 capsules and in unit dose blisters containing 28x1, 56x1 and 100x1 capsules.

Norvasc 10 mg capsules are available in blister packs containing 14, 28, 30, 56, 90, 98 and 100 capsules and in unit dose blisters containing 30x1, 56x1 and 100x1 capsules.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

[See Annex I - To be completed nationally]

Manufacturers
Pfizer Manufacturing Deutschland GmbH
Heinrick-Mack-Strasse 35
89257 Illertissen
Germany

Teva Czech Industries s.r.o.
Ostravská 29, č.p. 305
Opava-Komárov, 747 70
Czech Republic

Pfizer PGM, Zone Industrielle,
29 route des Industries,
37530 Pocé-sur-Cisse,
France

This medicinal product is authorised in the Member States of the EEA under the following names:
Tablets:
Austria, Bulgaria, Denmark, Estonia, Finland, Germany, Hungary, Italy, Latvia, Lithuania, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Sweden: Norvasc
Denmark: Amlodipine Pfizer
Ireland, Malta, United Kingdom: Istin
Ireland: Amlodipine besilate 5 mg tablets, Amlodipine besilate 10 mg tablets
Italy: Monopina
Spain : Norvas 5 mg comprimidos, Norvas 10 mg comprimidos;
Spain: Amlodipino Pharmacia 5 mg comprimidos, Amlodipino Pharmacia 10 mg comprimidos

Capsules:
Cyprus, Greece, Lithuania, Romania: Norvasc
Belgium, France, Luxembourg: Amlor

[See Annex I - To be completed nationally]

This leaflet was last approved in {MM/YYYY}.

[To be completed nationally]

Detailed information on this medicinal product is available on the website of {name of MS/Agency}

[To be completed nationally]