

SCHEDULING STATUS: **S3**

1. NAME OF THE MEDICINE

NORVASC® TABLETS 5 mg

NORVASC® TABLETS 10 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each NORVASC 5 mg tablet contains amlodipine besylate equivalent to 5 mg active amlodipine base.

Each NORVASC 10 mg tablet contains amlodipine besylate equivalent to 10 mg active amlodipine base.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

NORVASC 5 mg: White, emerald shaped tablets marked PFIZER on one side and AML-5 on the other.

NORVASC 10 mg: White, emerald shaped tablets marked PFIZER on one side and AML-10 on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertension

NORVASC is indicated for the treatment of mild to moderate hypertension. NORVASC may be combined with other antihypertensive medicines.

Coronary artery disease (CAD)

Angina pectoris

NORVASC is indicated for the treatment of angina pectoris.

Chronic stable angina

NORVASC is indicated for the first line treatment of myocardial ischaemia, whether due to fixed obstruction

(stable angina) and/or vasospasm/vasoconstriction (Prinzmetal's or variant angina) of coronary vasculature. NORVASC may be used alone, as monotherapy, or in combination with other antianginal medicines.

Coronary artery disease

NORVASC is indicated to reduce the risk of coronary revascularisation and the need for hospitalisation due to angina in patients with coronary artery disease.

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

4.2 Posology and method of administration

Posology

Hypertension and angina pectoris

The 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 after 10 – 14 days therapy.

No dose adjustment of NORVASC is required during combined administration of thiazide diuretics, beta blockers, or angiotensin converting enzyme inhibitors.

Coronary artery disease

The recommended dosage range is 5 – 10 mg once daily. In clinical studies, the majority of patients required 10 mg.

Special populations

Use in the 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 section 4.4).

Use in patients with hepatic function 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). The pharmacokinetics of NORVASC have not been studied in severe hepatic impairment. NORVASC should be initiated at the lowest dose and titrated slowly in patients with severe hepatic

impairment.

Use in patients with renal impairment

Changes in NORVASC plasma concentrations are not correlated with degree of renal impairment; therefore the normal dosage is recommended. NORVASC is not dialysable.

Paediatric population

The recommended antihypertensive oral dose in paediatric 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 paediatric patients.

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

Method of administration

For oral use.

4.3 Contraindications

NORVASC is contraindicated in patients with:

- Hypersensitivity to dihydropyridines derivatives, amlodipine or to any of the excipients listed in section 6.1.
- Concomitant use with grapefruit juice (see section 4.5).
- 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

Concomitant use with potent cytochrome CYP3A4 medicines

The blood pressure lowering effect may be enhanced when potent CYP3A4 inhibitors such as ketoconazole, itraconazole or ritonavir are co-administered (see section 4.5).

Use in the elderly

The time to reach peak plasma concentrations of NORVASC is variable and not significantly different between elderly and younger subjects. NORVASC clearance is decreased with resulting increases in AUC (40 – 60 %) and elimination half-life in elderly patients. AUC and elimination half-life in patients with

congestive heart failure (CHF) were increased with age. Elderly patients should start NORVASC therapy at a lower dose. Increase of the dosage should take place with care (see section 4.2).

Use in patients with renal failure

NORVASC may be used at normal doses in patients with renal impairment. Changes in amlodipine plasma concentrations are not correlated with the degree of renal impairment. NORVASC is not dialysable.

Use in patients with impaired hepatic function

The half-life of NORVASC is prolonged in patients with impaired liver function; dosage recommendations have not been established. NORVASC should therefore be administered at lower (5 mg) initial dose in these patients 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 patients with heart failure

In a long-term, placebo-controlled study (PRAISE-2) of NORVASC in patients with New York Heart Association (NYHA) class III and IV heart failure of non-ischaemic aetiology, NORVASC was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo.

Sodium

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction

NORVASC has been administered with thiazide diuretics, alpha blockers, beta blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerine, non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics, and oral hypoglycaemic medicines.

In vitro data from studies with human plasma indicate that NORVASC has no effect on protein binding of the medicines tested (digoxin, phenytoin, warfarin, or indomethacin).

Simvastatin

Co-administration of multiple doses of 10 mg NORVASC with simvastatin resulted in a 77 % increase in exposure to simvastatin compared to simvastatin alone (see simvastatin professional information).

Grapefruit juice

Co-administration of 240 mL of grapefruit juice with a single oral dose of NORVASC 10 mg in 20 healthy

volunteers had no significant effect on the pharmacokinetics of NORVASC. The study did not allow examination of the effect of genetic polymorphism in CYP3A4, the primary enzyme responsible for metabolism of NORVASC; therefore, administration of NORVASC with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients, resulting in increased blood pressure lowering effects (see section 4.3).

CYP3A4 inhibitors

Co-administration of a 180 mg daily dose of diltiazem with 5 mg NORVASC in elderly hypertensive patients (69 to 87 years of age) resulted in a 57 % increase in NORVASC systemic exposure and a significant further decrease in systolic blood pressure than with NORVASC alone.

Strong inhibitors of CYP3A4 (e.g. ketoconazole, itraconazole, ritonavir) may increase the plasma concentrations of NORVASC. NORVASC should be used with caution when administered with CYP3A4 inhibitors (see section 4.4).

Clarithromycin

Clarithromycin is an inhibitor of CYP3A4. There is an increased risk of hypotension in patients receiving clarithromycin with NORVASC. Close observation of patients is recommended when NORVASC is co-administered with clarithromycin.

There is no information on the effect of the combination on the QT interval.

CYP3A4 inducers

There is no data available regarding the effect of CYP3A4 inducers on NORVASC. Concomitant use of CYP3A4 inducers (e.g. rifampicin, *hypericum perforatum*) may decrease the plasma concentrations of NORVASC. NORVASC should be used with caution when administered with CYP3A4 inducers.

In the following studies, there were no significant changes in the pharmacokinetics of either NORVASC or another medicine within the study, when co-administered.

Special studies: Effect of other medicines on NORVASC

Cimetidine

Co-administration with cimetidine did not alter the pharmacokinetics of NORVASC.

Aluminium/magnesium (antacid)

Co-administration of an aluminium/magnesium antacid with a single dose of NORVASC had no significant effect on the pharmacokinetics of NORVASC.

Sildenafil

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

Special studies: Effect of NORVASC on other medicines

Digoxin

Co-administration of NORVASC with digoxin did not change serum digoxin levels or digoxin renal clearance in healthy volunteers.

Ethanol (alcohol)

Single and multiple 10 mg doses of NORVASC had no significant effect on the pharmacokinetics of ethanol.

Warfarin

Co-administration of NORVASC with warfarin did not change the warfarin prothrombin response time.

Ciclosporin

No medicine interaction studies have been conducted with ciclosporin and NORVASC in healthy volunteers or other populations, with the exception of renal transplant patients. Various studies in renal transplant patients report that co-administration of NORVASC with ciclosporin increased the trough concentrations of ciclosporin and increased ciclosporin toxicity, from no change up to an average increase of 40 %. Consideration should be given for monitoring ciclosporin levels in renal transplant patients on NORVASC.

Tacrolimus

There is a risk of increased tacrolimus blood levels and toxicity when co-administered with NORVASC. In order to avoid toxicity of tacrolimus, administration of NORVASC in a patient treated with tacrolimus requires monitoring of tacrolimus blood levels and dose adjustment of tacrolimus when appropriate.

Mechanistic target of rapamycin (mTOR) inhibitors

mTOR inhibitors such as sirolimus, temsirolimus and everolimus are CYP3A substrates. NORVASC is a weak CYP3A inhibitor. With concomitant use of mTOR inhibitors, NORVASC may increase exposure of mTOR inhibitors.

Medicine/laboratory test interactions

None known.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/ Contraception in males and females

Women of childbearing potential and their partners should be advised to ensure adequate contraceptive cover.

Pregnancy

The safety of NORVASC in human pregnancy has not been established.

In animal studies, reproductive toxicity was observed at high doses.

Breastfeeding

NORVASC is excreted in human milk. The proportion of the maternal dose received by the infant has been estimated with an interquartile range of 3 – 7 %, with a maximum of 15 %. The effect of NORVASC on infants is unknown.

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 NORVASC on fertility.

There was no effect on the fertility of rats treated with NORVASC (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 NORVASC 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.

*Based on patient weight of 50 kg

4.7 Effects on ability to drive and use machines

NORVASC can cause dizziness. The patient's ability to drive or use machinery should be individually assessed.

4.8 Undesirable effects

Tabulated summary of adverse reactions

The following adverse events, listed according to the system organ class have been categorised as follows:

Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1\ 000$ to $< 1/100$); rare ($\geq 1/10\ 000$ to $< 1/1\ 000$); very rare ($< 1/10\ 000$).

| MedDRA System Organ Class | Frequency | Undesirable effects |
|--|------------------|--|
| <i>Blood and lymphatic system disorders</i> | Uncommon | Leukopenia, thrombocytopenia |
| <i>Immune system disorders</i> | Rare | Allergic reaction including pruritus, rash, angioedema and erythema multiforme |
| <i>Metabolism and nutrition disorders</i> | Uncommon | Hyperglycaemia |
| <i>Psychiatric disorders</i> | Uncommon | Insomnia, mood changes |
| <i>Nervous system disorders</i> | Common | Somnolence, dizziness, headache |
| | Uncommon | Tremor, dysgeusia, syncope, hypoaesthesia, paraesthesia, hypertonia, peripheral neuropathy, extrapyramidal disorder |
| <i>Eye disorders</i> | Uncommon | Visual impairment |
| <i>Ear and labyrinth disorders</i> | Uncommon | Tinnitus |
| <i>Cardiac disorders</i> | Common | Palpitations |
| | Very rare | Myocardial infarction, arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation), chest pain |
| <i>Vascular disorders</i> | Common | Flushing |
| | Uncommon | Hypotension, Vasculitis |
| <i>Respiratory, thoracic and mediastinal disorders</i> | Uncommon | Dyspnoea, rhinitis, cough |
| <i>Gastrointestinal disorders</i> | Common | Abdominal pain, nausea |

| | | |
|---|-----------|--|
| | Uncommon | Vomiting, dyspepsia (including gastritis), altered bowel habits, dry mouth, pancreatitis, gingival hyperplasia |
| <i>Hepatobiliary disorders</i> | Very rare | Hepatitis, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis) |
| <i>Skin and subcutaneous tissue disorders</i> | Uncommon | Alopecia, purpura, skin discolouration, hyperhidrosis, pruritus, rash |
| | Very rare | Angioedema, erythema multiforme, urticaria |
| <i>Musculoskeletal and connective tissue disorders</i> | Uncommon | Arthralgia, myalgia, muscle spasms, back pain |
| <i>Renal and urinary disorders</i> | Uncommon | Micturition disorder, nocturia, pollakiuria |
| <i>Reproductive system and breast disorders</i> | Uncommon | Erectile dysfunction, gynaecomastia |
| <i>General disorders and administration site conditions</i> | Common | Oedema, fatigue |
| | Uncommon | Asthenia, pain, malaise |
| <i>Investigations</i> | Uncommon | Weight increase, weight decrease |

Paediatric population

Paediatric patients (ages 6 – 17 years)

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

| MedDRA System Organ Class | Undesirable effects |
|---|----------------------------|
| <i>Nervous system disorders</i> | Headaches, dizziness |
| <i>Vascular disorders</i> | Vasodilation |
| <i>Respiratory, thoracic, and mediastinal disorders</i> | Epistaxis |
| <i>Gastrointestinal disorders</i> | Abdominal pain |
| <i>General disorders and administration site conditions</i> | Asthenia |

Severe adverse events (predominantly headache) were experienced by 7,2 % with NORVASC 2,5 mg,

4,5 % with NORVASC 5 mg, 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the “**6.04 Adverse Drug Reactions Reporting Form**”, found online under SAHPRA’s publications: <https://www.sahpra.org.za/Publications/Index/8>.

4.9 Overdose

Symptoms

Available data for NORVASC suggest that gross overdosage could result in excessive peripheral vasodilation 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 NORVASC overdosage may need active cardiovascular support, including frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output.

Non-cardiogenic pulmonary oedema has rarely been reported as a consequence of NORVASC overdose that may manifest with a delayed onset (24 – 48 hours post-ingestion) and require ventilatory support. Early resuscitative measures (including fluid overload) to maintain perfusion and cardiac output may be precipitating factors.

Treatment is symptomatic and supportive. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.

Administration of activated charcoal to healthy volunteers immediately after or up to 2 hours after NORVASC 10 mg ingestion has been shown to significantly decrease NORVASC absorption. Activated charcoal given 6 hours after NORVASC had no effect.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 7.1 Vasodilators, hypotensive, antihypertensive medicines include other antihypertensive medicines e.g. ACE-inhibitors, ARBs, RAAS, etc

Mechanism of action

Amlodipine is a dihydropyridine, calcium ion influx inhibitor (calcium 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 in experimental animals, amlodipine reduces total ischaemic burden by the following action:

Amlodipine dilates peripheral arterioles and thus reduces the total peripheral resistance (afterload) against which the heart works. Unloading of the heart reduces myocardial energy consumption and oxygen requirements.

5.2 Pharmacokinetic properties

Absorption

After oral administration of therapeutic doses, amlodipine is absorbed with peak blood levels between 6 and 12 hours post dose. Absolute bioavailability has been estimated to be approximately 64 %. The volume of distribution is approximately 21 L/kg. Absorption of amlodipine is unaffected by consumption of a low-fat breakfast.

In vitro studies have shown that approximately 97,5 % of circulating amlodipine is bound to plasma proteins.

Biotransformation/elimination

The terminal plasma elimination half-life is about 35 – 50 hours. Steady state plasma levels are reached after 7 – 8 days of consecutive dosing.

Amlodipine is extensively metabolised by the liver to inactive metabolites. 10 % of the parent compound and 60 % of the metabolites are excreted in the urine.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Dibasic calcium phosphate anhydrous

Magnesium stearate

Microcrystalline cellulose

Sodium starch glycollate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 30 °C.

Protect from light.

6.5 Nature and contents of container

NORVASC 5 mg and 10 mg are available strip packed in blister packs in outer cardboard cartons each containing 30, 60 and 90 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Viatrix Healthcare (Pty) Ltd

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Isando

Gauteng, 1609

Tel.: +27(011) 451 1300 / +27(071) 281 2503 (24 hours)

Manufactured by: Pfizer Pharmaceuticals Limited, 22 Daqing Road, Economic & Technical Development
Zone, Dalian, P.R. China, 116600

8. REGISTRATION NUMBERS

NORVASC TABLETS 5 mg: Y/7.1/26

NORVASC TABLETS 10 mg: Y/7.1/27

9. DATE OF FIRST AUTHORISATION

NORVASC TABLETS 5 mg and 10 mg: 26 November 1991

10. DATE OF REVISION OF THE TEXT

19 February 2024

BOTSWANA: S2

NORVASC TABLETS 5 mg – Reg. no.: B9316370

NORVASC TABLETS 10 mg – Reg. no.: BOT9800295

NAMIBIA: NS2

NORVASC TABLETS 5 mg – Reg. no.: 04/7.1/1228

NORVASC TABLETS 10 mg – Reg. no.: 04/7.1/1229

ZAMBIA: POM

NORVASC TABLETS 5 mg – Reg. no.: 120/013

ZIMBABWE: PP10

NORVASC TABLETS 5 mg – Reg. no.: 90/12.6/2422

NORVASC TABLETS 10 mg – Reg. no.: 90/12.6/2423