SCHEDULING STATUS: S3

PROPRIETARY NAME AND DOSAGE FORM:

NORVASC® TABLETS 5 mg

NORVASC® TABLETS 10 mg

COMPOSITION:

NORVASC (amlodipine besylate) is a dihydropyridine derivative and has the following chemical name: 3-ethyl 5-methyl 2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridine-dicarboxylate benzene sulphonate.

Amlodipine besylate is slightly soluble in water and sparingly soluble in ethanol and has a molecular weight of 567,1 (free base 408,9).

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.

Excipients:

NORVASC TABLETS include the following inert ingredients: dibasic calcium phosphate anhydrous, magnesium stearate, microcrystalline cellulose and sodium starch glycollate.

PHARMACOLOGICAL CLASSIFICATION:

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

PHARMACOLOGICAL ACTION:

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 smooth muscle without changing serum calcium concentrations.

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 ischemic 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.

Amlodipine binds to dihydropyridine binding sites. It has a minimal effect on cardiac conduction, contraction or heart rate.

After oral administration of therapeutic doses, amlodipine is absorbed with peak blood levels between 6 – 12 hours post dose. Oral bioavailability is about 64 %. The volume of distribution is approximately 20 l/kg. 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 with 90 % converted to inactive metabolites. 10 % of the parent compound and 60 % of the metabolites are excreted in the urine.

INDICATIONS:

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

NORVASC is indicated for the treatment of angina pectoris.

CONTRAINDICATIONS:

NORVASC is contraindicated in patients with a known sensitivity to dihydropyridines, amlodipine, or any of the inert ingredients.

Safety of NORVASC in human pregnancy or lactation has not been established.

WARNINGS AND SPECIAL PRECAUTIONS:

Use in the elderly:

Elderly patients may have higher plasma concentrations of amlodipine than those in the younger patients. The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger

subjects. Amlodipine clearance is decreased with resulting increases in AUC (approximately 40 – 60 %) and elimination half-life in elderly and hepatically insufficient patients. A similar increase in AUC was observed in patients with moderate to severe heart failure. Elderly patients should start on a lower dose.

Use in renal failure:

Amlodipine is extensively metabolised to inactive metabolites with 10 % excreted unchanged in the urine. Changes in amlodipine plasma concentrations are not correlated with mild renal impairment. NORVASC may be used in such patients at normal doses. In patients with severe renal impairment, amlodipine dosages may need to be reduced. Amlodipine is not dialysable.

Use in patients with impaired hepatic function:

Amlodipine half-life is prolonged in patients with impaired liver function. NORVASC should therefore be administered at lower (5 mg) initial dose in these patients.

Use in children:

Safety and effectiveness of amlodipine in children has not been established.

Compatibility with other medicines:

NORVASC may be administered with thiazide diuretics, beta blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerine, nonsteroidal anti-inflammatory drugs, antibiotics, and oral hypoglycaemic medicines.

Studies have indicated that the co-administration of NORVASC with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers, and that co-administration of cimetidine did not alter the pharmacokinetics of NORVASC.

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

In healthy male volunteers, the co-administration of amlodipine does not significantly alter the effect of warfarin on prothrombin response time.

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

DOSAGE AND DIRECTIONS FOR USE:

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 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.

SIDE EFFECTS:

The most commonly observed side effects were headache, oedema, fatigue, somnolence, nausea, flushing, palpitations and dizziness. Vomiting and abdominal pain have occurred.

Less commonly observed side effects include alopecia, altered bowel habits, arthralgia, asthenia, back pain, dyspepsia, dyspnoea, gingival hyperplasia, gynecomastia, hyperglycaemia impotence, increased urinary frequency, leucopenia, malaise, mood changes and depression, dry mouth, muscle cramps, myalgia, peripheral neuropathy, pancreatitis, increased sweating, syncope, thrombocytopenia, vasculitis and visual disturbances.

Allergic reactions including pruritus, rash, angioedema and erythema multiforme have also been observed.

The following adverse events have been reported but cannot be distinguished from the natural history of the underlying disease: myocardial infarction, arrhythmia (including ventricular tachycardia and atrial fibrillation) and chest pain.

Hepatitis and jaundice and hepatic enzyme elevations have been reported (mostly consistent with cholestasis). Some cases severe enough to require hospitalisation have been reported in association with use of amlodipine.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

There is no well documented experience with amlodipine overdosage. Gastric lavage may be worthwhile. Available data suggest that gross overdosage could result in excessive peripheral vasodilation with subsequent marked and probably prolonged systemic hypotension. Clinically significant hypotension due to amlodipine overdosage calls for active cardiovascular support. 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.

IDENTIFICATION:

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

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

PRESENTATION:

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

STORAGE INSTRUCTIONS:

Store at or below 30 °C. Protect from light. Keep out of the reach of children.

REGISTRATION NUMBERS:

NORVASC TABLETS 5 mg: Y/7.1/26

NORVASC TABLETS 10 mg: Y/7.1/27

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Upjohn South Africa (Pty) Ltd

85 Bute Lane

Sandton

2196

South Africa

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

23 January 2001

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.: 90/12.3.1/2422

NORVASC TABLETS 10 mg – Reg. no.: 90/12.3.1/2423