SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Amlodipine 10 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Ingredient: amlodipine.

One tablet contains amlodipine besilate equivalent to 10 mg amlodipine.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

The tablets are white, circular, biconvex and plain on both sides.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Essential hypertension
- Chronic stable and vasospastic anginal pectoris

4.2 Posology and method of administration

In adults

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

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

Use in children

Children with hypertension from 6 years to 17 years of age.

The recommended antihypertensive oral dose in pediatric 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 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

The 2.5 mg dose cannot be obtained with Amlodipine tablets 5 mg as these tablets are not manufactured to break into two equal halves

Use in the elderly

Amlodipine, used at similar doses in elderly or younger patients, is equally well tolerated. Therefore normal dosage regimens are recommended.

Patients with hepatic impairment

See section 4.4 "Special warnings and special precautions for use".

Patients with 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.

4.3 Contraindications

Hypersensitivity to dihydropyridines, amlodipine or to any of the excipients.

Amlodipine should not be used in cardiogenic shock, clinically significant aortic stenosis, unstable angina (excluding Prinzmetal's angina).

Pregnancy and lactation.

4.4 Special warnings and precautions for use

Use in patients with heart failure

In a long term, placebo controlled study, in patients with NYHA III and IV heart failure of nonischaemic aetiology, amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo. See section 5.1 (Pharmacodynamic Properties).

Use in patients with impaired hepatic function

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

There are no data to support the use of amlodipine alone, during or within one month of a myocardial infarction.

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

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 glyceryl trinitrate, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycaemic drugs.

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

Caution should be exercised in combination of amlodipine and CYP3A4 inhibitors and CYP3A4 inducers.

Special Studies: Effect of other agents on amlodipine

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

Grapefruit juice*:* Administartion 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.

Sildenafil*:* When amlodipine and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

Special Studies: Effect of amlodipine on other agents

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

Digoxin*: Co-administration* of amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers.

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

Drug/Laboratory test interactions: None known.

4.6 Pregnancy and lactation

Pregnancy

Although some dihydropyridine compounds have been found to be teratogenic in animals, data in the rat and rabbit for amlodipine provide no evidence for a teratogenic effect. There is, however, no clinical experience with the preparation in pregnancy. Accordingly, amlodipine should not be administered during pregnancy or to women of childbearing potential unless effective contraception is used (see section 4.3).

Lactation

Although some dihydropyridine compounds have been found to be teratogenic in animals, data in the rat and rabbit for amlodipine provide no evidence for a teratogenic effect. There is, however, no clinical experience with the preparation in lactation. Accordingly, amlodipine should not be administered during lactation (see section 4.3).

4.7 Effects on ability to drive and use machines

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

In patients suffering from dizziness, headache, fatigue or nausea the ability to react may be impaired.

4.8 Undesirable effects

The frequencies mentioned are subdivided on categories according to following percentages:
Very common: more then 10%
Common: 10% or less, but more then 1% Uncommon: 1%, or less, but more then 0,1%,
Rare: 0,1 % or less, but more then 0,01%
Very rare: 0,01% and less (this includes isolated reports).

The most commonly reported side effects of amlodipine are headache, oedema, rash, fatigue, nausea, flushing and dizziness.

Other reported side effects are:

Blood and the lymphatic system disorders
Very rare: thrombocytopenia, leucocytopenia

Immune system disorders
Very rare: allergic reaction

Metabolic and nutrition disorders
Very rare: hyperglycaemia

Psychiatric disorders
Uncommon: mood changes, insomnia

Nervous system disorders
Common: somnolence
Uncommon: tremor, taste perversion, syncope, hypoaesthesia, paraesthesia Very rare: peripheral neuropathy

Eye disorders
Uncommon: visual disturbances

Ear and Labyrinth disorders
Uncommon: tinnitus

Cardiac disorders Common: Palpitations Rare: syncope
Very rare: Myocardial infarction, arrhythmia, ventricular tachycardia and atrial fibrillation

Vascular disorders
Uncommon: hypotension
Very rare: vasculitis

Respiratory, thoracic and mediastinal disorders
Uncommon: dyspnoea, rhinitis Very rare: coughing

Gastrointestinal disorders
Common: Abdominal pain
Uncommon: Vomiting, dyspepsia, altered bowel habits, dry mouth Very rare: pancreatitis, gastritis, gingival hyperplasia

Hepato-biliary disorders
Very rare: abnormal liver function tests, hepatitis, jaundice,

Skin and subcutaneous tissue disorders
Uncommon: alopecia, pruritus, perpura, skin discolouration, increased sweating
Very rare: erythema multiforme, angioedema and urticaria

Musculoskeletal, connective tissue and bone disorders
Uncommon: myalgia, arthralgia, muscle cramps and back pain

Renal and urinary disorders
Uncommon: increased urinary frequency, micturition disorder, nocturia

Reproductive system and breast disorders
Uncommon: impotence, gynaecomastia

General disorders and administration site conditions
Uncommon: chest pain, asthenia, pain, malaise, increase or decrease in weight

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

In humans, experience with intentional overdose is limited. Gastric lavage may be worthwhile in some cases. Available data suggest that gross overdosage (> 100 mg) could result in excessive peripheral vasodilatation with subsequent marked and probably prolonged systemic hypotension. 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. In healthy volunteers, the use of charcoal up to 2h 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 – Dihydropyridine derivatives.

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.

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.

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.

Haemodynamic 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 ACE inhibitors has shown that amlodipine 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) in patients with NYHA III and IV heart failure without clinical symptoms or objective findings suggestive of underlying ischaemic disease, on stable doses of ACE inhibitors, digitalis, and diuretics, amlodipine had no effect on total cardiovascular mortality. In this same population amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo.

In a study involving 268 children aged 6-17 years with predominantly secondary hypertension, comparison of a 2.5mg dose, and 5.0mg 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.

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 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 12 month 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 13-17 years of age the typical oral clearance (CL/F) was 22.5 and 27.4 L/hr respectively in males and 16.4 and 21.3 L/hr respectively in females. Large variability in exposure between individuals was observed. Data reported in children below 6 years is limited.

5.3 Preclinical safety data

None.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose (E460)

Sodium starch glycollate

Sodium acid citrate (E331)

Magnesium stearate (E572)

Croscarmellose sodium

Crospovidone

6.2 Incompatibilities

None stated.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

No special precautions for storage.

Store in the original packaging.

6.5 Nature and contents of container

Blisters made of aluminium foil with VMCH coating (a carboxyl modified vinyl copolymer) on one side and amber coloured PVC foil. Packs of 28 tablets.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Somex Pharma

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Ilford, Essex, IG3 8BS

UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 15764/0016

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