SCHEDULING STATUS:

S3

PROPRIETARY NAME AND DOSAGE FORM:

KEYSAL 5 mg (Tablets)

KEYSAL 10 mg (Tablets)

COMPOSITION:

KEYSAL 5 mg: Each tablet contains amlodipine besilate equivalent to amlodipine 5 mg.

KEYSAL 10 mg: Each tablet contains amlodipine besilate equivalent to amlodipine 10 mg.

Excipients: Cellulose microcrystalline; sodium starch glycolate; calcium hydrogen phosphate anhydrous and magnesium stearate.

PHARMACOLOGICAL CLASSIFICATION:

A 7.1 Vasodilators, hypotensive medicines.

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Amlodipine is a dihydropyridine calcium channel blocker. It inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle without affecting serum calcium concentrations. Direct relaxation of vascular smooth muscles forms the basis of the antihypertensive action.

In angina pectoris, amlodipine acts a peripheral arteriolar vasodilator resulting in a reduction in total peripheral resistance (afterload). Myocardial energy and oxygen requirements are reduced.

Amlodipine exerts its activity by binding to the dihydropyridine binding sites. It exerts minimal action on cardiac conduction, contraction and heart rate.

Pharmacokinetic properties:

Complete absorption of amlodipine is slow following oral administration with peak plasma levels being attained after 6 to 12 hours. Amlodipine has a bioavailability of about 64 % and a plasma elimination half-life of 35 to 50 hours, allowing for once-daily oral dosing. Steady state plasma

concentrations are achieved after 7 to 8 days of consecutive dosing. The volume of distribution is about 20 l/kg. Metabolism is via the liver and is extensive with less than 10 % of amlodipine appearing unchanged in the urine. Metabolites are inactive and primarily (up to 60 %) excreted via the kidney.

INDICATIONS:

KEYSAL is indicated for the:

- Treatment of angina pectoris.
- Treatment of mild-to-moderate hypertension, alone or in combination with other antihypertensives.

CONTRAINDICATIONS:

Hypersensitivity to any of the ingredients.

Hypersensitivity to dihydropyridines.

WARNINGS and SPECIAL PRECAUTIONS:

The substitutability or interchangeability with other amlodipine containing products has not been established.

Use in the Elderly:

Amlodipine clearance is decreased (40 – 60 %) in the elderly, which results in increases of amlodipine concentration in the area under the concentration-time curve (AUC) and elimination half-life. Therefore, elderly patients should start **KEYSAL** therapy at a lower dose.

Use in Renal Failure:

Although **KEYSAL** is excreted primarily via the kidney, mild renal impairment does not appear to have an effect on the plasma concentrations. Severe renal impairment may however require a dosage reduction. **KEYSAL** is not dialysable.

Use in Impaired Hepatic Function

The half-life of **KEYSAL** is significantly prolonged in patients with impaired hepatic function. **KEYSAL** should therefore be administered at lower doses in these patients.

Use in Children

Safety and efficacy has not been established.

Use in Heart Failure

An increased incidence of pulmonary oedema has been reported.

KEYSAL may have a negative inotropic effect. AUC in **KEYSAL** may increase in patients with heart failure.

Porphyria: Safety has not been established.

INTERACTIONS:

Concurrent administration of sublingual nitroglycerin, long acting nitrates, beta-blockers or other antianginal agents with amlodipine may produce additive antihypertensive and antianginal effects. Sublingual nitroglycerin may be used as needed to abort acute angina attacks during amlodipine therapy. Nitrate medication may be used during amlodipine therapy for angina prophylaxis.

Amlodipine will not protect against the consequences of abrupt beta-blocker withdrawal; gradual beta-blocker dose reduction is recommended.

Although no 'rebound effect' has been reported upon discontinuation of amlodipine, a gradual decrease of dosage with medical practitioner supervision is recommended.

PREGNANCY AND LACTATION:

Safety in pregnancy and lactation has not been established (see "**CONTRAINDICATIONS"**).

DOSAGE AND DIRECTIONS FOR USE:

Hypertension and Angina Pectoris:

Adults:

An initial dosage of 5 mg **KEYSAL** once daily is recommended which may be increased to 10 mg once a day after 10-14 days of therapy if there is no improvement.

No dose reduction is required when adding **KEYSAL** to thiazide diuretics, beta-blockers, or angiotensin converting enzyme inhibitors.

SIDE EFFECTS:

Cardiac disorders

Frequent: peripheral oedema, angioedema, palpitations.

Less frequent: syncope, vasculitis.

The following side effects have been reported and frequencies are unknown: hypotension (including orthostatic hypotension), myocardial infarction, arrhythmia (including ventricular tachycardia and atrial fibrillation), chest pain.

Nervous system disorders

Frequent: dizziness, headache, somnolence, flushing.

Less frequent: mood changes, dry mouth, peripheral neuropathy, increased sweating.

The following side effects have been reported and frequencies are unknown: hypertonia, hypoesthesia/paraesthesia, tremor, insomnia, increased sweating, pain.

Gastrointestinal disorders

Frequent: nausea, abdominal pain, vomiting.

Less frequent: altered bowel habits, dyspepsia, gingival hyperplasia, pancreatitis.

The following side effects have been reported and frequencies are unknown: taste perversion.

Musculoskeletal, connective tissue and bone disorders

Frequent: fatigue.

Less frequent: arthralgia, asthenia, back pain, muscle cramps, myalgia.

Hepato-biliary disorders

The following side effects have been reported and frequencies are unknown: hepatitis, jaundice.

Blood and lymphatic system disorders

Less Frequent: leucopenia, thrombocytopenia.

The following side effects have been reported and frequencies are unknown: purpura.

Renal and urinary disorders

Less frequent: increased urinary frequency.

Reproductive system and breast disorders

Less frequent: impotence.

Endocrine disorders

Less frequent: gynaecomastia.

The following side effects have been reported and frequencies are unknown: weight increase/decrease.

Investigations

Less frequent: hypoglycaemia.

The following side effects have been reported and frequencies are unknown: raised liver enzymes (mostly consistent with cholestasis).

Skin and subcutaneous tissue disorders

Less frequent: alopecia.

The following side effects have been reported and frequencies are unknown: allergic reactions with pruritus, rash, and erythema multiforme.

Respiratory, thoracic and mediastinal disorders

Less frequent: dyspnoea.

The following side effects have been reported and frequencies are unknown: coughing.

Eye disorders

Less frequent: visual disturbances.

Ear and labyrinth disorders

The following side effects have been reported and frequencies are unknown: tinnitus.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

There is no documented experience with **KEYSAL** overdosage. Gastric lavage may be of benefit. Gross overdosage could result in excessive peripheral vasodilation, resulting in marked and probably prolonged systematic hypotension.

Clinically significant hypotension due to **KEYSAL** overdosage requires active cardiovascular support. Intravenous calcium gluconate may be of benefit in reversing the effects of calcium channel blockade. Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

TREATMENT IS SYMPTOMATIC AND SUPPORTIVE.

IDENTIFICATION:

KEYSAL 5 mg

White to off white, flat, bevel edged, barrel shaped uncoated tablets, debossed with ‘C’ on one side and ‘58’ on the other side.

KEYSAL 10 mg

White to off white, flat, bevel edged, round shaped uncoated tablets, debossed with ‘C’ on one side and ‘59’ on the other side.

PRESENTATION:

KEYSAL 5 mg:

PVC/PE/Aclar-Alu Blister Pack:

Tablets are packed in 250 micron white opaque PVC film laminated with 25 micron PE coated with 23 micron Aclar and 25 microns Printed Aluminium foil. Each blister contains 10 tablets.

Pack size: 30's- Each carton contains 3 blisters of 10 tablets each.

PVC/PVdC -Alu Blister Pack:

Tablets are packed in 250 micron white opaque PVC film laminated with 90 gsm PVdC and 25 microns Printed Aluminium foil. Each blister contains 10 tablets.

Pack size: 30's- Each carton contains 3 blisters of 10 tablets each.

KEYSAL 10 mg

PVC/PE/Aclar-Alu Blister Pack:

Tablets are packed in 250 micron white opaque PVC film laminated with 25 micron PE coated with 23 micron Aclar and 25 microns Printed Aluminium foil. Each blister contains 10 tablets.

Pack size: 30's- Each carton contains 3 blisters of 10 tablets each.

PVC/PVdC -Alu Blister Pack:

Tablets are packed in 250 micron white opaque PVC film laminated with 90 gsm PVdC and 25 microns Printed Aluminium foil. Each blister contains 10 tablets.

Pack size: 30's- Each carton contains 3 blisters of 10 tablets each.

STORAGE INSTRUCTIONS:

Store at or below 30 °C.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

KEYSAL 5 mg: 41/7.1/0749

KEYSAL 10 mg: 41/7.1/0750

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

Novagen Pharma (Pty) Ltd.

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