APPROVED PACKAGE INSERT:

AUSTELL-SIMVASTATIN 10/20/40 mg

SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

AUSTELL–SIMVASTATIN 10 mg TABLETS

AUSTELL–SIMVASTATIN 20 mg TABLETS

AUSTELL–SIMVASTATIN 40 mg TABLETS

COMPOSITION

Austell-Simvastatin 10 mg:

Each film coated tablet contains simvastatin 10 mg.

Austell-Simvastatin 20 mg:

Each film coated tablet contains simvastatin 20 mg.

Austell-Simvastatin 40 mg:

Each film coated tablet contains simvastatin 40 mg.

The tablets contain the following as preservatives:

Butylated hydroxytoluene 0.02% m/m

Ascorbic acid 2.04 % m/m.

PHARMACOLOGICAL CLASSIFICATION

A 7.5 Serum-cholesterol reducers.

PHARMACOLOGICAL ACTION

Simvastatin is a cholesterol-lowering agent derived synthetically from a fermentation product of *Aspergillus terreus*. After oral ingestion, simvastatin, an inactive lactone, is hydrolysed to the corresponding beta-hydroxyacid, the active form. This is a principal metabolite and an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the enzyme that catalyses the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in the biosynthesis of cholesterol. As a result, simvastatin, reduces total plasma cholesterol, low-density lipoprotein (LDL)- and very low-density lipoprotein (VLDL)-cholesterol concentrations. Apolipoprotein B is also decreased. In addition, simvastatin moderately increases high density lipoprotein (HDL)-cholesterol and variably reduces plasma triglycerides.

Pharmacokinetics:

There is extensive first-pass extraction by the liver, with oral bioavailability of the active medicine or metabolites being less than 5 %. More than 95 % of simvastatin and its beta-hydroxy metabolite are bound to plasma proteins. Following an oral dose, peak plasma concentrations of simvastatin are seen in 1 to 2 hours. Simvastatiin is excreted primarily via the liver, and less than 13 % of its metabolites are excreted in the urine.

INDICATIONS

Hypercholesterolaemia:

AUSTELL-SIMVASTATIN tablets are indicated, in combination with diet, to decrease elevated serum total cholesterol and LDL-cholesterol in patients with:

- Primary hypercholesterolaemia,
- Heterozygous familial hypercholesterolaemia, or
- Mixed hyperlipidaemia

when response to diet or other nonpharmacological measures alone is not adequate.

Coronary heart disease:

AUSTELL-SIMVASTATIN tablets are indicated in patients with coronary heart disease and hypercholesterolaemia unresponsive to diet, to:

- Reduce the risk of total mortality, by reducing coronary death,
- Reduce the risk of non-fatal myocardial infarction,
- Reduce the risk of undergoing myocardial revascularisation procedures (coronary artery bypass grafting and percutaneous transluminal coronary angioplasty), and
- Slow the progression of coronary atherosclerosis.

CONTRA-INDICATIONS

Hypersensitivity to simvastatin, other HMG-CoA reductase inhibitors, or any of the ingredients.

Acute or chronic liver disease.

Unexplained persistent elevations of serum transaminases.

Pregnancy and lactation (see warnings).

Porphyria: Safety has not been established.

WARNINGS

The active metabolite of **AUSTELL-SIMVASTATIN** is fetotoxic and teratogenic in rats, and it should therefore not be used in female patients of child-bearing potential. Use in paediatric patients is not recommended, as safety and efficacy have not been established.

INTERACTIONS

Myopathy caused by medicine interactions:

Concomitant administration of medicines that inhibit cytochrome P450 isoenzyme CYP3A4 may result in high plasma levels of **AUSTELL-SIMVASTATIN**, thus increasing the risk of myopathy, and is not recommended. Medicines that inhibit cytochrome P450 isoenzyme CYP3A4 include: cyclosporine, itraconazole, ketoconazole, erythromycin, clarithromycin, HIV-protease inhibitors and nefazodone.

The risk of myopathy is increased when other medicines that cause myopathy, such as fibrates and niacin, are given with **AUSTELL-SIMVASTATIN**. A maximum dose of 10 mg **AUSTELL-SIMVASTATIN** daily is recommended in patients taking cyclosporine, fibrates or lipid lowering doses of niacin (nicotinic acid).

Digoxin:

AUSTELL-SIMVASTATIN may cause increases in digoxin levels.

Coumarin-derivatives (e.g. Warfarin):

A possible increase in the anticoagulant effect of the coumarin anticoagulants may occur. Patients taking coumarin anticoagulant should have their INR determined before starting **AUSTELL-SIMVASTATIN** therapy. The INR should be monitored frequently enough in the early stages of therapy until stabilised. Once a stable INR has been documented, INR can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. When there is a dose adjustment of **AUSTELL-SIMVASTATIN**, this procedure should be repeated.

Bile acid sequestrants:

AUSTELL-SIMVASTATIN should be taken 1 hour before or 4 hours after cholestyramine. Concurrent use may decrease the bioavailability of **AUSTELL-SIMVASTATIN**.

PREGNANCY AND LACTATION

Safety in pregnancy and lactation has not been established. The active metabolite of **AUSTELL-SIMVASTATIN** is fetotoxic and teratogenic in rats, and it should therefore not be used in female patients of child-bearing potential.

DOSAGE AND DIRECTIONS FOR USE

The patient must follow a cholesterol-lowering diet before initiation of, and while on **AUSTELL-SIMVASTATIN** therapy.

Hypercholesterolaemia

Adults: Initial dose: 10 mg daily as a single dose in the evening.

The dose of **AUSTELL-SIMVASTATIN** should be reduced if LDL-cholesterol levels fall below 1.94 mmol/l, or total plasma cholesterol levels fall below 3,6 mmol/l.

Coronary heart disease

Adults: Initial dose: 20 mg/day as a single dose in the evening.

Dosage adjustments:

If required, the dose should be adjusted at intervals of not less than 4 weeks, up to a maximum of 80 mg daily as a single dose in the evening.

AUSTELL-SIMVASTATIN can be taken with meals or on an empty stomach.

Dosage in renal insufficiency

AUSTELL-SIMVASTATIN does not undergo significant renal excretion, therefore modification of dose should be necessary with mild to moderate renal insufficiency. In patients with severe renal insufficiency **AUSTELL-SIMVASTATIN** therapy should be closely monitored and doses above 10 mg/day should be implemented with caution.

CONCOMITANT THERAPY

AUSTELL-SIMVASTATIN is effective alone or in combination with bile acid sequestrants. When both medicines are prescribed, **AUSTELL-SIMVASTATIN** should be given 1 hour before or 4 hours after cholestyramine administration (See **INTERACTIONS**). A maximum daily dose of 10 mg **AUSTELL-SIMVASTATIN** is recommended in patients taking cyclosporine, fibrates or niacin concomitantly (See **INTERACTIONS**).

SIDE-EFFECTS AND SPECIAL PRECAUTIONS

Side-effects:

Gastro-intestinal

Constipation, diarrhoea, nausea, vomiting, flatulence, dyspepsia, abdominal pain, cramps and pancreatitis.

Haematological

Anaemia, neutropenia.

Skin and appendages

Skin rash, alopecia.

Musculoskeletal

- *Frequent*: Myalgia, muscle cramps.
- *Less Frequent*: Myopathy, myositis, rhabdomyolysis presenting as muscle pain with elevated creatine phosphokinase and myoglobinuria leading to renal failure.

Neurological

Headache, dizziness, fatigue, aesthaenia, paraesthesia, peripheral neuropathy.

Hypersensitivity reactions

Less frequent: reactions may include angioedema, lupus-like syndrome, polymyalgia rheumatica, vasculitis, thrombocytopenia, increased erythrocyte sedimentation rate, eosinophilia, arthritis, arthralgia, urticaria, photosensitivity, fever, flushing, malaise and dyspnoea.

Other

Mass gain has been reported.

Laboratory test findings

Marked and persistent increases of serum transaminases and elevated alkaline phosphatase and gamma-glutamyl transpeptidase have been reported. Liver function test abnormalities have generally been mild and transient. Increases in serum creatine kinase (CK) levels, derived from skeletal muscle, have been reported (See **SPECIAL PRECAUTIONS**).

Special precautions:

AUSTELL-SIMVASTATIN should be used with caution in patients who:

- Consume substantial amounts of alcohol and/or who have a history of liver disease.
- May be predisposed to developing renal failure secondary to rhabdomyolysis such as in those with severe acute infection, hypotension, severe metabolic, endocrine or electrolyte disorders, uncontrolled seizures, major surgery or trauma. There is an increased risk of developing renal failure if rhabdomyolysis occurs.
- Have severe renal impairment.

Hepatic effects

Liver function tests, including serum transaminase determinations are recommended pprior to initiation of **AUSTELL-SIMVASTATIN** therapy and periodically until one year after the last elevation in dose. **AUSTELL-SIMVASTATIN** should be discontinued if the

rise in transaminase levels is persistent and/or increases to three times or more the upper limit of normal (ULN).

Myopathy

Reducing the risk of myopathy:

1. General measures: Patients starting therapy with **AUSTELL-SIMVASTATIN** should be advised of the risk of myopathy and should report, promptly, unexplained muscle pain, tenderness or weakness. A creatine kinase (CK) level above 10 times the Upper Limit of Normal (ULN) in a patient, with unexplained symptoms, indicates myopathy. **AUSTELL-SIMVASTATIN** should be discontinued if myopathy is diagnosed or suspected.
2. Measures to reduce the risk of myopathy caused by medicine interactions:
   The benefits and risks of using **AUSTELL-SIMVASTATIN** concomitantly with immunosuppresants, fibrates or lipid-lowering doses of niacin should be carefully considered, and the dose of **AUSTELL-SIMVASTATIN** should generally not exceed 10 mg/day. Concomitant administration with cyclosporine, itraconazole, ketoconazole, erythromycin, clarithromycin, HIV-protease inhibitors and nefazodone, is not recommended. In patients receiving cyclosporine, **AUSTELL-SIMVASTATIN** should be temporarily discontinued if systemic azole derivative-antifungal therapy is required.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

(See **SIDE-EFFECTS AND SPECIAL PRECAUTIONS**)

General measures should be adopted and liver function should be monitored. Treatment is symptomatic and supportive.

IDENTIFICATION

AUSTELL–SIMVASTATIN 10 mg:

Pinkish Brown, oval, biconvex, film-coated tablets with ‘BL’ embossing on one side and ‘10’ embossing on the other side.

AUSTELL–SIMVASTATIN 20 mg:

Peach coloured, oval, biconvex, film-coated tablets with ‘BL’ embossing on one side and ‘20’ embossing on the other side.

AUSTELL–SIMVASTATIN 40 mg:

Dull pink coloured, oval, biconvex, film-coated tablets with ‘BL’ embossing on one side and ‘40’ embossing on the other side.

PRESENTATION

AUSTELL–SIMVASTATIN 10 mg:

Blister packs (White opaque PVDC coated PVC film and Aluminium foil) of 2 x 14 or 3 x 10 tablets.

AUSTELL–SIMVASTATIN 20 mg:

Blister packs (White opaque PVDC coated PVC film and Aluminium foil) of 2 x 14 or 3 x 10 tablets.

AUSTELL–SIMVASTATIN 40 mg:

Blister packs (White opaque PVDC coated PVC film and Aluminium foil) of 2 x 14 or 3 x 10 tablets.

STORAGE INSTRUCTIONS

Store in a dry place at or below 25 °C. Protect from light.

Keep blister packs in carton until required for use.

KEEP OUT OF REACH OF CHILDREN

REGISTRATION NUMBER

AUSTELL-SIMVASTATIN 10 mg: A38/7.5/0477

AUSTELL-SIMVASTATIN 20 mg: A38/7.5/0478

AUSTELL-SIMVASTATIN 40 mg: A38/7.5/0479

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

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