CURRENT APPROVED PROFESSIONAL INFOMRATION

SCHEDULING STATUS: S4

PROPRIETARY NAME (AND DOSAGE FORM):

CHOLESTE 10 (TABLET)

CHOLESTE 20 (TABLET)

CHOLESTE 40 (TABLET)

COMPOSITION:

Each **CHOLESTE 10** tablet contains 10 mg simvastatin.

Each **CHOLESTE 20** tablet contains 20 mg simvastatin.

Each **CHOLESTE 40** tablet contains 40 mg simvastatin.

Contains lactose.

Sucrose free.

Contains Butyl hydroxyl anisole 0,03% m/m as the antioxidant.

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. Simvastatin is excreted primarily via the liver, and less than 13 % of its metabolites are excreted in the urine.

INDICATIONS:

HYPERCHOLESTEROLAEMIA:

CHOLESTE is 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:

CHOLESTE is 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 **CHOLESTE** is fetotoxic and teratogenic in rats, and it should therefore not be used in female patients of childbearing 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 **CHOLESTE,** thus increasing the risk of myopathy, and is not recommended. Medicines that inhibit cytochrome P450 isoenzyme CYP3A4 include: cyclosporin, 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 **CHOLESTE**. A maximum dose of 10 mg **CHOLESTE** daily is recommended in patients taking cyclosporin, fibrates or lipid lowering doses of niacin (nicotinic acid).

Digoxin:

CHOLESTE 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 a coumarin anticoagulant should have their INR determined before starting **CHOLESTE** 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 **CHOLESTE,** this procedure should be repeated.

Bile acid sequestrants:

CHOLESTE should be taken 1 hour before or 4 hours after cholestyramine.

Concurrent use may decrease the bioavailability of **CHOLESTE.**

PREGNANCY AND LACTATION:

Safety in pregnancy and lactation has not been established.

The active metabolite of **CHOLESTE** 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 **CHOLESTE** therapy.

HYPERCHOLESTEROLAEMIA

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

The dose of **CHOLESTE** 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.

CHOLESTE can be taken with meals or on an empty stomach.

DOSAGE IN RENAL INSUFFICIENCY

CHOLESTE does not undergo significant renal excretion, therefore modification of dose should not be necessary in patients with mild to moderate renal insufficiency.

In patients with severe renal insufficiency **CHOLESTE** therapy should be closely monitored and doses above 10 mg/day should be implemented with caution.

CONCOMITANT THERAPY

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

SIDE – EFFECTS AND SPECIAL PRECAUTIONS:

Side-effects:

Blood and lymphatic system disorders:

- *Rare (> 1/10 000 and ≤ 1/1000):* Anaemia.
- *Incidence unknown:* Neutropaenia.

Metabolic and nutritional disorders:

- *Incidence unknown:* Mass gain has been reported.

Nervous system disorders:

- *Rare (> 1/10 000 and ≤ 1/1000):* Headache, dizziness, paraesthesia, peripheral neuropathy.
- *Incidence unknown:* Fatigue.

Gastrointestinal disorders:

- *Rare (> 1/10 000 and ≤ 1/1000):* Constipation, diarrhoea, nausea, vomiting, flatulence, dyspepsia, abdominal pain or cramps, pancreatitis.

Skin and subcutaneous tissue disorders:

- *Rare (> 1/10 000 and ≤ 1/1000):* Skin rash, alopecia.

Musculoskeletal, connective tissue and bone disorders:

- *Rare (> 1/10 000 and ≤ 1/1000):* Myalgia, muscle cramps, asthaenia, myopathy, rhabdomyolysis (presenting as muscle pain with elevated creatine phosphokinase and myoglobinuria leading to renal failure).
- *Incidence unknown:* Myositis.

General disorders and administration site conditions:

- *Rare (> 1/10 000 and ≤ 1/1000):* An apparent hypersensitivity syndrome has been reported. Reactions may include angioedema, lupus-like syndrome, polymyalgia rheumatica, vasculitis, thrombocytopaenia, increased erythrocyte sedimentation rate (ESR), eosinophilia, arthritis, arthralgia, urticaria, photosensitivity, fever, flushing, malaise, and dyspnoea.

Investigations:

Rare (> 1/10 000 and ≤ 1/1000): 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 creatinine kinase (CK) levels, derived from skeletal muscle, have been reported (see **"Special Precautions").**

SPECIAL PRECAUTIONS:

CHOLESTE 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 prior to initiation of **CHOLESTE** therapy and periodically until one year after the last elevation in dose. **CHOLESTE** 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:

General measures

Patients starting therapy with **CHOLESTE** should be advised of the risk of myopathy and should report, promptly, unexplained muscle pain, tenderness or weakness. A creatinine kinase (CK) level above 10 times the Upper Limit of Normal (ULN) in a patient, with unexplained symptoms, indicates myopathy. **CHOLESTE** should be discountinued if myopathy is diagnosed or suspected.

Measures to reduce the risk of myopathy caused by medicine interactions

The benefits and risks of using **CHOLESTE** concomitantly with immunosuppressants, fibrates or lipid-lowering doses of niacin should be carefully considered, and the dose of **CHOLESTE** should generally not exceed 10 mg/day. Concomitant administration with cyclosporin, itraconazole, ketoconazole, erythromycin, clarithromycin, HIV-protease inhibitors and nefazodone, is not recommended.

In patients receiving cyclosporin, **CHOLESTE** should be temporarily discontinued if systemic azole derivative-antifungal therapy is required.

KNOWN SYMPTOMS OF OVER-DOSAGE 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:

CHOLESTE 10: Light pink coloured, round shaped, biconvex film coated tablets, debossed with 'A' on one side and '01' on the other side.

CHOLESTE 20: Light pink coloured, round shaped, biconvex, film coated tablets, debossed with 'A' on one side and '02' on the other side.

CHOLESTE 40: Pink coloured, round shaped, biconvex, film coated tablets, debossed with 'A' on one side and '03' on the other side.

PRESENTATION:

CHOLESTE 10, CHOLESTE 20 and CHOLESTE 40:

30's:

Printed unit carton containing 3 blister packs (composed of either white opaque PVC / Aclar and silver coloured aluminium foil backing or white opaque triple laminate and silver coloured aluminium foil backing) of 10 tablets each.

28's:

Printed unit carton containing 2 blister packs (composed of either white opaque PVC / Aclar and silver coloured aluminium foil backing or white opaque triple laminate and silver coloured aluminium foil backing) of 14 tablets each.

STORAGE INSTRUCTIONS:

Store in a cool (at or below 30°C), dry place. Protect from light. Do not remove the blister packs from the unit carton until required for use.

STORE CHOLESTE TABLETS OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS:

Choleste 10: 41/7.5/0391

Choleste 20: 41/7.5/0392

Choleste 40: 41/7.5/0393

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

Unicorn Pharmaceuticals (Pty) Ltd.

Corner of Searle & Pontac Streets

Cape Town

8001

South Africa

DATE OF PUBLICATION OF THE PACKAGE INSERT:

5 October 2007