SCHEDULING STATUS: S4

PROPRIETARY NAME AND DOSAGE FORM:
ADCO SIMVASTATIN 10 mg (TABLET)
ADCO SIMVASTATIN 20 mg (TABLET)
ADCO SIMVASTATIN 40 mg (TABLET)

COMPOSITION:
Each **ADCO SIMVASTATIN 10 mg** tablet contains 10 mg simvastatin and butylhydroxianisole 0,02 % m/m as an antioxidant.
Contains sugar: Anhydrous lactose 74,5 mg.
List of excipients: hydroxypropyl cellulose, magnesium stearate, methylhydroxypropyl cellulose, microcrystalline cellulose, pregelatinised maize starch, purified talc, titanium dioxide.

Each **ADCO SIMVASTATIN 20 mg** tablet contains 20 mg simvastatin and butylhydroxianisole 0,02 % m/m as an antioxidant.
Contains sugar: Anhydrous lactose 149,0 mg.
List of excipients: hydroxypropyl cellulose, magnesium stearate, methylhydroxypropyl cellulose, microcrystalline cellulose, pregelatinised maize starch, purified talc, titanium dioxide.

Each **ADCO SIMVASTATIN 40 mg** tablet contains 40 mg simvastatin and butylhydroxianisole 0,02 % m/m as an antioxidant.
Contains sugar: Anhydrous lactose 298,0 mg.
List of excipients: hydroxypropyl cellulose, magnesium stearate, methylhydroxypropyl cellulose, microcrystalline cellulose, pregelatinised maize starch, purified talc, titanium dioxide.

PHARMACOLOGICAL CLASSIFICATION:
A: 7.5 Serum-cholesterol reducers

PHARMACOLOGICAL ACTION:
The cholesterol-lowering agent, simvastatin, is synthetically obtained from lovastatin, which is derived from a fermentation process. The inactive lactone, simvastatin, is hydrolyzed to beta-hydroxyacid (active form), after oral ingestion. Beta-hydroxyacid is a principal metabolite and inhibits 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the enzyme which catalyzes the conversion of HMG-CoA to mevalonate. This conversion is an early and rate limiting step in the production of cholesterol within the body. The effect of this inhibition, is that simvastatin reduces total plasma cholesterol, by decreasing very low-density lipoprotein (VLDL)- and low-density lipoprotein (LDL)-cholesterol concentrations, as well as apolipoprotein B and plasma triglyceride concentrations. An increase in high-density lipoprotein (HDL)-cholesterol concentrations is also noted.

INDICATIONS:

Hypercholesterolaemia

Reduction of elevated total and LDL-cholesterol levels in patients with primary hypercholesterolaemia, in whom response to diet and other non-pharmaceutical measures have been inadequate.

ADCO SIMVASTATIN is indicated to lower elevated cholesterol levels in patients with a combination of primary hypercholesterolaemia and primary hypertri-glyceridaemia, where the hypercholesterolaemia is of primary concern.

Coronary heart disease

Patients with established coronary heart disease and hypercholesterolaemia in whom dietary measures have been inadequate or ineffective.

- **ADCO SIMVASTATIN** is indicated to lower the risk of total mortality by decreasing coronary death, the risk of non-fatal myocardial infarction and the risk of undergoing myocardial revascularization procedures (coronary artery bypass grafting and percutaneous transluminal coronary angioplasty).
- **ADCO SIMVASTATIN** is also indicated to delay the progression of coronary atherosclerosis.

CONTRAINDICATIONS:

Hypersensitivity to simvastatin or any of the excipients used in the tablet.
Simvastatin should not be given to patients with acute liver disease or unexplained persistent raised serum-amino transferase concentrations or those with porphyria.
Pregnancy and lactation.

WARNINGS AND SPECIAL PRECAUTIONS:

Female patients of childbearing potential should not use **ADCO SIMVASTATIN**, as the active metabolite is fetotoxic and teratogenic in rats.
As safety and efficacy have not yet been established, use in paediatric patients is not advised.

ADCO SIMVASTATIN is ineffective for the treatment of homozygous familial hypertriglyceridaemia or hypercholesterolaemia.

Concomitant use of immunosuppressive medicines (especially cyclosporine), fibric acid derivatives and/or niacin with HMG-CoA reductase inhibitors has resulted in rhabdomyolysis, sometimes with acute renal failure.

Agents of the Statin Class FDA Class Warnings for Lipid Lowering

The following effects have been reported with medicines in this class; not all effects listed below have necessarily been associated with **ADCO SIMVASTATIN** therapy.
Skeletal: myopathy, muscle cramps, rhabdomyolysis, arthralgias, myalgia.

Neurological: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, dizziness, memory loss, vertigo, paraesthesia, peripheral neuropathy, peripheral nerve palsy, anxiety, insomnia, depression, psychic disturbances.
Hypersensitivity reactions: an apparent hypersensitivity syndrome has been reported that included one or more of the following features: anaphylaxis, angioedema, lupus erythematosus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, purpura, thrombocytopenia, leucopenia, haemolytic anaemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnoea, toxic epidermal necrolysis, erythema multiforme including Stevens Johnson syndrome.
Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, cirrhosis, fulminant hepatic necrosis and hepatoma, anorexia, vomiting.
Skin: alopecia, pruritus. A variety of skin changes, (e.g. nodules, discolouration, dryness of skin/mucous membranes, changes to hair/nails), have been reported.
Reproductive: gynaecomastia, loss of libido, erectile dysfunction.
Eye: progression of cataracts (lens opacities), ophthalmoplegia.
Laboratory abnormalities: elevated transaminases, creatine kinase, alkaline phosphatase, gamma-glutamyl transpeptidase and bilirubin, thyroid function abnormalities.

Hepatic effects
Marked, persistent elevations in serum transaminases (to more than 3 times the upper limit of normal) have occurred. Upon discontinuation or interruption of simvastatin treatment, the elevated transaminase levels in these patients slowly dropped to pretreatment levels.
All patients are advised to undergo liver function tests prior to initiation of therapy, and periodically thereafter, as hepatitis, an indicator of which is an increase in liver enzymes, has also been reported.
Caution should be exercised in patients who develop elevated serum transaminase levels. Measurements should be repeated promptly and then performed more frequently in such patients. Discontinue treatment with **ADCO SIMVASTATIN** if the transaminase levels continue to rise, particularly if they rise to three times the upper limit of normal and are persistent. Patients who consume substantial quantities of alcohol and/or have a history of liver disease should use **ADCO SIMVASTATIN** with caution. The use of simvastatin is contraindicated in patients with active liver diseases or in patients that have unexplained increases in transaminase levels.

Ophthalmic effects
An increase in the prevalence of lens opacities is expected with time as a result of ageing and not necessarily due to the use of simvastatin.
No relationship exists between the use of simvastatin and adverse effects on the human lens.

Muscle effects

Increased creatine kinase (CK) levels (from skeletal muscles) have been frequently reported. Marked elevations of CK, muscle tenderness and/or diffuse myalgia are symptoms of myopathy. This condition should be considered in any patient presenting with such symptoms. In addition, any unexplained muscle pain, tenderness or weakness should be reported immediately.

If there is a potential diagnosis of myopathy, or if there is a significant increase in CK levels, treatment with **ADCO SIMVASTATIN** should be discontinued immediately.

Concomitant use of **ADCO SIMVASTATIN** together with immunosuppressive agents including cyclosporine, fibric acid derivatives or lipid lowering doses of niacin (nicotinic acid) could increase the risk of myopathy. The risk / benefit profile of these combinations should therefore be carefully considered.

Patients on HMG-CoA reductase inhibitor therapy have experienced rhabdomyolysis with or without renal impairment. A renal transplant patient on cyclosporine and simvastatin experienced muscle fatigue together with a significant increase of CK, after the introduction of therapy with the systemic antifungal agent itraconazole. Cholesterol biosynthesis is inhibited at different stages in the biosynthetic pathway by the HMG-CoA reductase inhibitors and the azole derivative antifungal agents. Simvastatin treatment should therefore be temporarily discontinued in patients receiving cyclosporine and simvastatin, who also require systemic azole derivative antifungal therapy. Patients only receiving simvastatin require careful monitoring if systemic azole derivative antifungal therapy is initiated.

INTERACTIONS:

Coumarin derivatives

Simvastatin 20 to 40 mg/day slightly enhances the effect of coumarin anticoagulants, as indicated by the prothrombin times [reported as International Normalized Ratio (INR)], which increased from a baseline of 1,7 to 1,8 in normal volunteers and from a baseline of 2,6 to 3,4 in hypercholesterolaemic patients.

In order to ensure that no significant changes to prothrombin times occur in patients taking coumarin anticoagulants, the prothrombin time should be determined prior to starting simvastatin therapy and at frequent intervals during early treatment with simvastatin.

Prothrombin times may be monitored at the intervals usually indicated for patients on coumarin anticoagulants, once it has stabilised and been documented. Any dosage alterations to simvastatin should follow the same procedure. Patients taking simvastatin have not experienced bleeding or changes in prothrombin time, in the absence of anticoagulant therapy.

Digoxin

Simvastatin elevates digoxin levels.

Fibric acid derivatives

See **WARNINGS AND SPECIAL PRECAUTIONS – Muscle effects**.

Other concomitant therapy
ADCO SIMVASTATIN when used simultaneously with immunosuppressant therapy, itraconazole or niacin, should be monitored cautiously. (See **WARNINGS AND SPECIAL PRECAUTIONS – Muscle effects**).

Propranolol
Concomitant administration of a single dose of simvastatin and propranolol in healthy male volunteers, showed a significant decrease in mean $C_{max,}$ but no change in AUC, for simvastatin total and active inhibitors. The clinical importance of this finding is unclear. The enantiomers of propranolol remain unchanged in terms of their pharmacokinetic properties.

Mibefradil
Raised concentrations of simvastatin have also occurred in patients given mibefradil.

Laboratory test findings
Liver function test abnormalities have been mild and transient. Significant and persistent increases of serum transaminases, elevated serum creatine kinase (CK) levels (derived from skeletal muscle), elevated alkaline phophatase and elevated γ-glutamyl transpeptidase have been reported. (see **WARNINGS AND SPECIAL PRECAUTIONS**).

DOSAGE AND DIRECTIONS FOR USE:
Prior to, and throughout treatment with **ADCO SIMVASTATIN**, the patient should be placed on a standard cholesterol-lowering diet.

Hypercholesterolaemia
The usual initial dose is 10 mg/day given as a single dose in the evening. The dosage may be adjusted, if needed, but at intervals of not less than 4 weeks. The maximum dosage that may be given is 40 mg daily as a single dose in the evening.
If LDL-cholesterol levels fall below 1,94 mmol/l (75 mg/dl) or total plasma cholesterol levels fall below 3,6 mmol/l (140 mg/dl) consideration should be given to a reduction in dose of **ADCO SIMVASTATIN**.

Coronary heart disease
A starting dose of 20 mg/day may be given as a single dose in the evening.
The dosage may be adjusted, if needed, in accordance with the instructions under **'Hypercholesterolaemia'.**

Dosage in renal insufficiency
Patients with moderate renal insufficiency may not require dosage adjustments due to the fact that **ADCO SIMVASTATIN** does not undergo significant renal excretion.

Implementation of dosages above 10 mg/day require careful consideration and caution in patients with severe renal insufficiency (creatine clearance < 30 ml/min).

Concomitant therapy
ADCO SIMVASTATIN is effective as a single agent. It is also effective when used in combination with bile-acid sequestrants but it should be given either one hour prior to, or four hours after cholestyramine administration.
The lowest recommended dosage of HMG-CoA reductase inhibitors and immunosuppressive agents should be used if these drugs are taken together, as the incidence of myopathy in such patients has increased. (see **WARNINGS AND SPECIAL PRECAUTIONS – Muscle effects**).

SIDE EFFECTS:
Blood and the lymphatic system disorders:
Anaemia, neutropenia.

Immune system disorders:
There have been less frequent reports of an apparent hypersensitivity syndrome. Some of the features of this syndrome include: lupus-like syndrome, fever, malaise, vasculitis, polymyalgia rheumatica, angioedema, eosinophilia, thrombocytopenia, arthritis, urticaria, increased erythrocyte sedimentation rate, arthralgia, photosensitivity, flushing and dyspnoea.

Metabolism and nutrition disorders:
Mass gain.

Psychiatric disorders:
Insomnia.

Nervous system disorders:
Dizziness, paraesthesia, peripheral neuropathy.

Eye disorders:
Blurred vision.

Gastrointestinal disorders:
Abdominal pain, cramps, constipation, flatulence, nausea, diarrhoea, dyspepsia, vomiting, dysgeusia.
Pancreatitis has been reported less frequently.

Hepato-biliary disorders:
Hepatitis and jaundice have been reported less frequently.

Skin and subcutaneous tissue disorders:
Skin rashes, pruritus.

Musculoskeletal, connective tissue and bone disorders:
Muscle cramps, myalgia.
Rhabdomyolysis and myopathy have been reported less frequently.

General disorders and administrative site conditions:
Asthenia, headache, fatigue, alopecia.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT
(See **SIDE EFFECTS & WARNINGS AND SPECIAL PRECAUTIONS**)
General measures should be adopted and liver function tests should be performed.
Treatment of overdosage is symptomatic and supportive.

IDENTIFICATION:
ADCO SIMVASTATIN 10 mg tablets:
White, oblong, biconvex, film-coated tablets, scored on the one side. The tablets are debossed with “SVT” on the unscored side and “10” on the scored side.
ADCO SIMVASTATIN 20 mg tablets:
White, oblong, biconvex, film-coated tablets, scored on the one side. The tablets are debossed with “SVT” on the unscored side and “20” on the scored side.
ADCO SIMVASTATIN 40 mg tablets:
White, oblong, biconvex, film-coated tablets, scored on the one side. The tablets are debossed with “SVT” on the unscored side and “40” on the scored side.

PRESENTATION:
ADCO SIMVASTATIN 10 mg, 20 mg & **40 mg** tablets:
The white blister packs of PVC/PE/PVDC/Al and the blister packs of PVC/PE/PVDC/Al in Al sachets, are both available as cartons of 10, 20, 30, 50 or 100 tablets, where the tablets are enclosed in blister strips of 10 tablets or 15 tablets each. The white blister packs of PVC/PE/PVDC/Al and the blister packs of PVC/PE/PVDC/Al in Al sachets, are also available as cartons of 14 or 28 tablets, where the tablets are enclosed in blister strips of 14 tablets each. The 300 ml white HDPE tablet containers with child resistant polypropylene closures contain 100 or 300 tablets.
Not all pack sizes will be marketed.

STORAGE INSTRUCTIONS:
Keep well closed. Keep blister in carton until required for use.
Store in a dry place, at or below 25 °C in the original package.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:
ADCO SIMVASTATIN 10 mg: 35/7.5/0277
ADCO SIMVASTATIN 20 mg: 35/7.5/0278
ADCO SIMVASTATIN 40 mg: 35/7.5/0279

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