SCHEDULING STATUS: S4

PROPRIETARY NAMES AND DOSAGE FORMS:
SANDOZ PRAVASTATIN 10 (tablets)
SANDOZ PRAVASTATIN 20 (tablets)
SANDOZ PRAVASTATIN 40 (tablets)

COMPOSITION:
Each Sandoz Pravastatin 10 tablet contains: 10 mg Pravastatin sodium.
Each Sandoz Pravastatin 20 tablet contains: 20 mg Pravastatin sodium.
Each Sandoz Pravastatin 40 tablet contains: 40 mg Pravastatin sodium.
Contains lactose.

PHARMACOLOGICAL CLASSIFICATION:
A 7.5 Serum-cholesterol reducers

PHARMACOLOGICAL ACTION:
Pravastatin is a cholesterol-lowering agent derived synthetically from a fermentation product of *Aspergillus terreus*. Pravastatin is active without the need for hydrolysis. Pravastatin is a competitive 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, pravastatin reduces total plasma cholesterol, low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) cholesterol concentrations. Apolipoprotein B is also decreased. In addition, pravastatin moderately increases high-density lipoprotein (HDL) cholesterol and variably reduces plasma triglycerides.

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

INDICATIONS:
Hypercholesterolaemia:
SANDOZ PRAVASTATIN 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 non-pharmacological measures alone are not adequate.

Coronary heart disease (prevention):
SANDOZ PRAVASTATIN 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.

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 SANDOZ PRAVASTATIN, this procedure should be repeated.

Bile acid sequestrants:
SANDOZ PRAVASTATIN should be taken 1 hour before or 4 hours after cholestyramine.
Concurrent use may decrease the bioavailability of SANDOZ PRAVASTATIN.

PREGNANCY AND LACTATION:
Safety in pregnancy and lactation has not been established. The active metabolite of SANDOZ PRAVASTATIN is fetotoxic and teratogenic in rats, and it should therefore not be used in female patients of child-bearing potential (see "WARNINGS AND SPECIAL PRECAUTIONS").

DOSAGE AND DIRECTIONS FOR USE:
The patient must follow a cholesterol-lowering diet before initiation of, and while on SANDOZ PRAVASTATIN therapy.

Hypercholesterolaemia:
Adults initial dose: 10 mg daily as a single dose in the evening.
The dose of SANDOZ PRAVASTATIN 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 per 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. SANDOZ PRAVASTATIN can be taken with meals or on an empty stomach.

Dosage in renal insufficiency:
SANDOZ PRAVASTATIN 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 SANDOZ PRAVASTATIN therapy should be closely monitored and doses above 10 mg per day should be implemented with caution.

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

SIDE EFFECTS:
Gastrointestinal:
Frequent: Constipation, diarrhoea, nausea, vomiting, flatulence, dyspepsia, abdominal pain, cramps.
Less frequent: Pancreatitis.

Haematological:
Less frequent: Anaemia, neutropenia.

CONTRA-INDICATIONS:

- Hypersensitivity to SANDOZ PRAVASTATIN, 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 AND SPECIAL PRECAUTIONS" and "PREGNANCY AND LACTATION").
- Porphyria: Safety has not been established.

WARNINGS AND SPECIAL PRECAUTIONS:

The active metabolite of SANDOZ PRAVASTATIN 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 (see "PREGNANCY AND LACTATION").

SANDOZ PRAVASTATIN 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 SANDOZ PRAVASTATIN therapy and periodically until one year after the last elevation in dose. SANDOZ PRAVASTATIN 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 SANDOZ PRAVASTATIN 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. SANDOZ PRAVASTATIN 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 SANDOZ PRAVASTATIN concomitantly with immunosuppresants, fibrates or lipid-lowering doses of niacin should be carefully considered, and the dose of SANDOZ PRAVASTATIN generally not exceed 10 mg per day. Concomitant administration with cyclosporin, itraconazole, ketoconazole, erythromycin, clarithromycin, HIV-protease inhibitors and nefazodone is not recommended.
In patients receiving cyclosporin, SANDOZ PRAVASTATIN should be temporarily discontinued if systemic azole derivative-antifungal therapy is required.

Lactose intolerance:

SANDOZ PRAVASTATIN contains lactose; therefore it should not be used by patients with rare hereditary problems of lactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

INTERACTIONS:

Myopathy caused by medicine interactions:

Concomitant administration of medicines that inhibit cytochrome P450 isoenzyme CYP3A4 may result in high plasma levels of SANDOZ PRAVASTATIN, 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 (see "WARNINGS AND SPECIAL PRECAUTIONS").

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

Digoxin:

SANDOZ PRAVASTATIN may cause an increase 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 SANDOZ PRAVASTATIN therapy. The INR

Skin and appendages:

Frequent: Skin rash.
Less frequent: 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.

Central nervous system:

Frequent: Headache, dizziness.
Less frequent: Fatigue, 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:

Less frequent: Mass gain.

Laboratory test findings:

Less frequent: Marked and persistent increase 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 "WARNINGS AND SPECIAL PRECAUTIONS").

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

(See "SIDE EFFECTS" and "WARNINGS AND SPECIAL PRECAUTIONS".)
General measures should be adopted and liver function should be monitored.
Treatment is symptomatic and supportive.

IDENTIFICATION:

Sandoz Pravastatin 10: Light brown, mottled, oval tablet, scored on both sides and debossed with "P 10" on one side.
Sandoz Pravastatin 20: Light brown, mottled, oval tablet, scored on both sides and debossed with "P 20" on one side.
Sandoz Pravastatin 40: Light brown, mottled, oval tablet, scored on both sides and debossed with "P 40" on one side.

PRESENTATION:

Sandoz Pravastatin tablets are available in aluminium/aluminium blister packs of 30 tablets.

STORAGE INSTRUCTIONS:

Store in the original packs at or below 25 °C. Protect from moisture and light.
KEEP OUT OF THE REACH OF CHILDREN.

REGISTRATION NUMBERS:

Sandoz Pravastatin 10: A39/7.5/0300
Sandoz Pravastatin 20: A39/7.5/0301
Sandoz Pravastatin 40: A39/7.5/0302

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

Sandoz SA (Pty) Ltd[1]
72 Steel Road, Spartan
Kempton Park, 1619
South Africa

DATE OF PUBLICATION OF THE PACKAGE INSERT:

01 December 2006

Additional countries registration details:

Botswana		
Sandoz Pravastatin 10 (tablets)	S2	BOT1202066
Sandoz Pravastatin 20 (tablets)	S2	BOT1202065
Sandoz Pravastatin 40 (tablets)	S2	BOT1202064
Namibia		
Sandoz Pravastatin 10 (tablets)	NS2	14/7.5/0048
Sandoz Pravastatin 20 (tablets)	NS2	14/7.5/0047
Sandoz Pravastatin 40 (tablets)	NS2	14/7.5/0046

ATC Code: C10AA03 – HMG CoA reductase inhibitors

Name and address of manufacturer:
Lek Pharmaceuticals D.D
Verovškova 57, 1526 Ljubljana
Slovenia

[1]Company Reg. No.: 1990/001979/07