PROFESSIONAL INFORMATION

Scheduling status: S4

Proprietary name and dosage form:

Lipidex 10 film-coated tablets

Lipidex 20 film-coated tablets

Composition:

Each Lipidex 10 film-coated tablet contains: 10 mg simvastatin.

Each Lipidex 10 film-coated tablet contains:

0.02 mg Butylhydroxyanisole (0.014 % m/m) and 2,5 mg ascorbic acid (1,75 % m/m) as antioxidant.

Contains sugar (lactose monohydrate 95.2 mg).

Each Lipidex 20 film-coated tablet contains 20 mg simvastatin.

Each Lipidex 20 film-coated tablet contains:

0.04 mg Butylhydroxyanisole (0.014 % m/m) and 5,0 mg ascorbic acid (1,75 % m/m) as antioxidant.

Contains sugar (lactose monohydrate 190.0 mg).

List of excipients:

Tablet core:

Ascorbic acid, butylhydroxyanisole, citric acid monohydrate,

lactose monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinized starch.

Film-coating:

Hypromellose, titanium dioxide (E171), talc, iron oxide red (E172), iron oxide yellow (E172).

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:

LIPIDEX 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:

LIPIDEX 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 LIPIDEX 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 LIPIDEX, 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 LIPIDEX. A maximum dose of 10 mg LIPIDEX daily is recommended in patients taking cyclosporin, danazol, fibrates or lipid lowering doses of niacin (nicotinic acid).

Concurrent use of verapamil with LIPIDEX may be associated with an increased risk of myopathy; this effect has not been seen with other calcium channel blockers.

Grape fruit juice:

Concurrent use of LIPIDEX with large volumes of grape fruit juice may significantly increase the plasma concentrations of simvastatin and increase the risk of myopathy

Digoxin:

LIPIDEX 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 LIPIDEX 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 LIPIDEX, this procedure should be repeated.

Bile acid sequestrants:

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

Concurrent use may decrease the bioavailability of LIPIDEX.

Pregnancy and lactation:

Safety in pregnancy and lactation has not been established.

The active metabolite of LIPIDEX 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 LIPIDEX therapy.

Hypercholesterolaemia:

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

The dose of LIPIDEX 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.

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

Dosage in renal insufficiency:

LIPIDEX 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 LIPIDEX therapy should be closely monitored and doses above 10 mg/day should be implemented with caution.

Concomitant therapy:

LIPIDEX effective alone or in combination with bile acid sequestrants.

When both medicines are prescribed, LIPIDEX should be given 1 hour before or 4 hours after cholestyramine administration (see “Interactions”). A maximum daily dose of 10 mg LIPIDEX is recommended in patients taking cyclosporin, danazol, fibrates or niacin concomitantly (see “Interactions”).

Side-effects and special precautions:

Side-effects:

Gastrointestinal:

Frequent: Constipation, diarrhoea, nausea, flatulence, abdominal pain.

The following have been reported and the frequencies are unknown:

Vomiting, dyspepsia and pancreatitis.

Haematological:

The following have been reported and the frequencies are unknown:

Anaemia, neutropenia.

Skin and appendages:

Frequent: Skin rash.

The following has been reported and the frequency is unknown:

Alopecia.

Musculoskeletal:

Less frequent: Myalgia, myositis, rhabdomyolysis presenting as muscle pain with elevated creatine phosphoskinase and myoglobinuria leading to renal failure.

The following have been reported and the frequencies are unknown:

Myopathy, muscle cramps.

Neurological:

Frequent: Headache, dizziness.

The following have been reported and the frequencies are unknown:

Fatigue, asthenia, paraesthesia, peripheral neuropathy.

Immune system disorders:

The following have been reported and the frequencies are unknown:

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

General disorders:

The following has been reported and the frequency is unknown:

Mass gain.

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 creatinine kinase (CK) levels, derived from skeletal muscle, have been reported (see “Special precautions”).

Special precautions:

LIPIDEX 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 LIPIDEX therapy and periodically until one year after the last elevation in dose. LIPIDEX 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 LIPIDEX 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. LIPIDEX 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 LIPIDEX concomitantly with immunosuppressants, fibrates or lipid-lowering doses of niacin should be carefully considered, and the dose of LIPIDEX should generally not exceed 10 mg/day. Concomitant administration with cyclosporin, danazol, itraconazole, ketoconazole, erythromycin, clarithromycin, HIV-protease inhibitors and nefazodone, is not recommended.

In patients receiving cyclosporine, LIPIDEX 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:

Lipidex 10:

A peach-coloured, coated, oval, scored, convex tablet. Code SIM 10 on one side. Size:

Approximately 9.8mm x 5mm

Lipidex 20:

An orange-coloured coated, oval, scored, convex tablet. Code SIM 20 on one side. Size:

Approximately 11.7mm x 6mm.

Presentation:

White opaque polyethylene (HDPE) containers and closures (tamper evident) containing 28 or 30 tablets or white opaque PVC/aluminium blister packs containing 28 or 30 tablets per carton.

Storage instructions:

Polyethylene (HDPE) containers and closures:

Keep container tightly closed. Store in a dry place, at or below 25°C. Protect from light.

White opaque PVC/aluminium blister packs:

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

Do not remove the blisters from the outer carton until required for use.

KEEP OUT OF THE REACH OF CHILDREN

Registration numbers:

Lipidex 10: 36/7.5/0213

Lipidex 20: 36/7.5/0214

Name and business address of the holder of the certificate of registration:

Oethmaan Biosims (Pty) Ltd.

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