Downsterolin
(10/20 and 10/40) mg
Film-coated tablets

Generic Name: Ezetimibe + simvastatin (10/20) - (10/40) mg.
Dosage Form: Film-coated tablets.
Company: Medizen Pharmaceutical Industries for Utopia Pharmaceuticals.

Composition:
Each film-coated tablet contains:
Active Ingredients:
Ezetimibe
10mg.
Simvastatin
20 or 40mg.
Inactive Ingredients:
Magnesium stearate
- silicon dioxide colloidal - citric acid anhydrous – lactose - maize
starch -
povidone K - carboxy methyl cellulose sodium - polyethylene glycol 6000 - titanium dioxide.

Pharmacological Action:
Downsterolin is composed of ezetimibe and simvastatin, two lipid-lowering compounds with complementary mechanisms of action. **Downsterolin** reduces elevated total-C, LDL-C, Apo B, TG, and non-HDL-C, and increases HDL-C through dual inhibition of cholesterol absorption and synthesis.
Ezetimibe, a selective inhibitor of intestinal cholesterol, decreases the delivery of intestinal cholesterol to the liver. **Ezetimibe** had no clinically meaningful effect on the plasma concentrations of the fat-soluble vitamins A, D, and E.
Simvastatin reduces cholesterol by inhibiting the conversion of HMG-CoA to mevalonate, an early step in the biosynthetic pathway for cholesterol. In addition, simvastatin reduces VLDL and TG and increases HDL-C.

Pharmacokinetics:
Absorption: **Downsterolin** is bioequivalent to coadministered ezetimibe and simvastatin. After oral administration, ezetimibe is absorbed and extensively conjugated to a pharmacologically active phenolic glucuronide (ezetimibe-glucuronide). Simvastatin: Relative to the fasting state, the plasma profiles of both active and total inhibitors of HMG-CoA reductase were not affected when simvastatin was administered immediately before recommended low-fat meal.
Distribution: Ezetimibe and ezetimibe-glucuronide are highly bound (>90%) to human plasma proteins. Both simvastatin and its (beta)-hydroxyacid metabolite are highly bound (approximately 95%) to human plasma proteins.
Metabolism and Excretion: Ezetimibe is primarily metabolized in the small intestine and liver via glucuronide conjugation with subsequent biliary and renal excretion. Simvastatin is a lactone that is readily hydrolyzed in vivo to the corresponding (beta)-hydroxyacid, a potent inhibitor of HMG-CoA reductase. The major active metabolites of simvastatin present in human plasma are the (beta)-hydroxyacid of simvastatin and its 6'-hydroxy, 6'-hydroxymethyl, and 6'-exomethylene derivatives. Since simvastatin undergoes extensive first-pass extraction in the liver, the availability of the drug to the general circulation is low (<5%).

Indications and Usage:
Primary Hypercholesterolemia:
Downsterolin
is indicated as adjunctive therapy to diet for the reduction of elevated total-C, LDL-C, Apo B, TG, and non-HDL-C, and to increase HDL-C in patients with primary (heterozygous familial and non-familial) hypercholesterolemia or mixed hyperlipidemia.
Homozygous Familial Hypercholesterolemia (HoFH): **Downsterolin** is indicated for the reduction of elevated total-C and LDL-C in patients with homozygous familial hypercholesterolemia, as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.

Dosage and Administration:
Downsterolin should be taken as a single daily dose in the evening, with or without food. The dosage range is 10/10 mg/day through 10/80 mg/day. The recommended usual starting dose is 10/20 mg/day. Initiation of therapy with 10/10 mg/day may be considered for patients requiring less aggressive

LDL-C reductions. Patients who require a larger reduction in LDL-C (greater than 55%) may be started at 10/40 mg/day. After initiation or titration of **Downsterolin**, lipid levels may be analyzed after 2 or more weeks and dosage adjusted, if needed.

Patients with Homozygous Familial Hypercholesterolemia: The recommended dosage for patients with homozygous familial hypercholesterolemia is **Downsterolin** 10/40 mg/day in the evening.

Patients with Hepatic Insufficiency: No dosage adjustment is necessary in patients with mild hepatic insufficiency.

Contraindications:

Hypersensitivity to any component of this medication.

Active liver disease or unexplained persistent elevations in serum transaminases.

Pregnancy and Nursing Mothers:

As safety in pregnant women has not been established, treatment should be immediately discontinued as soon as pregnancy is recognized. Women who are nursing should not take **Downsterolin**.

Adverse Reactions:

Headache, influenza-like symptoms, upper respiratory tract infections, myalgia, pain in the extremities, fatigue, urticaria, arthralgia, myalgia, elevations in liver transaminases, thrombocytopenia, pancreatitis, nausea, dizziness, cholelithiasis, cholecystitis, elevated creatine phosphokinase, cataract, abdominal pain, constipation, diarrhea, dyspepsia, flatulence, eczema, pruritus, rash, muscle cramps, tremors, memory loss, paresthesia, peripheral neuropathy,
psychic disturbances, vertigo, anxiety, insomnia, depression, lupus erythematous-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia,
ESR increase, arthritis, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, gynecomastia, erectile dysfunction
and very rarely, myopathy /rhabdomyolysis.

Drug Interactions:

No clinically significant pharmacokinetic interaction was seen when ezetimibe was coadministered with simvastatin. **Cyclosporine** has been shown to increase the AUC of HMG-CoA reductase inhibitors. **Potent inhibitors of CYP3A4** can raise the plasma levels of HMG-CoA reductase. **Cholestyramine** decreased the mean AUC of total ezetimibe. **Fenofibrate** increased the mean Cmax and AUC values of total ezetimibe. Gemfibrozil increased bioavailability of total ezetimibe. **Grapefruit** increases in active and total HMG-CoA reductase inhibition. Large quantities of grape fruit should be avoided.

Precautions:

Hepatic Insufficiency: Downsterolin is not recommended in patients with moderate or severe hepatic insufficiency.

CYP3A4 Interactions: Potent inhibitors of CYP3A4 increase the risk of myopathy by reducing the elimination of the simvastatin component of
Downsterolin.

Digoxin: Patients taking digoxin should be monitored appropriately when **Downsterolin** is initiated.

Warfarin: Simvastatin 20-40 mg/day modestly potentiated the effect of coumarin.

Propranolol: Decrease in mean Cmax for simvastatin total and active inhibitors with concomitant administration of single doses of simvastatin and propranolol was observed.

Warnings:

Myopathy/Rhabdomyolysis: There was no excess of myopathy or rhabdomyolysis associated with ezetimibe. Simvastatin, like other inhibitors of HMG-CoA reductase, occasionally causes myopathy manifested as muscle pain, tenderness or weakness with creatine kinase above 10 X ULN. **Downsterolin** therapy should be discontinued immediately if myopathy is diagnosed or suspected. The use of **Downsterolin** concomitantly with the potent CYP3A4 inhibitors itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, nefazodone should be avoided. The combined use of **Downsterolin** at doses higher than 10/20 mg daily with amiodarone or verapamil should be avoided. It is recommended that liver function tests be performed before the initiation of treatment with **Downsterolin** and thereafter when clinically indicated.

Package:

Downsterolin 10/20 mg: Carton box containing 2 pvdc/aluminum strips; each strip has 14 film-coated tablets with the insert leaflet.

Downsterolin 10/40 mg: Carton box containing 2 pvdc/aluminum strips; each strip has 14 film-coated tablets with the insert leaflet.

Storage:

Keep out of reach of children.

Keep at a temperature not exceeding 30°C in a dry place away from light.

Instructions for Patients:

1- The patient should be placed on a standard cholesterol-lowering diet before receiving Downsterolin and should continue on this diet during treatment with Downsterolin.

2- Downsterolin should be taken at the same time every day.
3- Keep taking Downsterolin unless your doctor tells you to stop.
4- Periodic CK determination may be considered in patients starting therapy with simvastatine.

Produced by Medizen Pharmaceutical Industries for Utopia Pharmaceuticals