MEDOSTATIN® 20mg and 40mg Tablets
Lovastatin

Presentation
Tablets containing 20 or 40mg Lovastatin.
MEDOSTATIN 20mg Tablets are blue, round, flat, scored on one side and 8mm in diameter
MEDOSTATIN 40mg Tablets are white, round, flat, scored on one side and 8mm in diameter
(Lovastatin is butanoic acid-2-methyl-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2(tetrahydro-4hydroxy-6-oxo-2H-pyran-2yl)ethyl]-1-naphthalenyl ester[1S[1a®*),3a,7β,8β,(25*,45*)8aβ]]

Category:
Lovastatin is an antihyperlipidemic agent classified as an HMG-CoA reductase inhibitor.

Indications
MEDOSTATIN (lovastatin) is indicated for the reduction of elevated total and LDL-cholesterol levels in patients with primary hypercholesterolemia, when response to the diet and other non- pharmacological measures alone has been inadequate. It is also indicated for the reduction of elevated cholesterol levels in patients with combined hypercholesterolemia and hypertriglyceridemia, when the hypercholesterolemia is the abnormality of most concern.

Pharmacology
Pharmacodynamics
MEDOSTATIN (lovastatin) is a cholesterol lowering agent isolated from a strain of Aspergillus terreus. After oral ingestion lovastatin, which is an inactive lactone, is hydrolyzed to the corresponding β-hydroxy acid form. This is a principal metabolite and an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate limiting step in the biosynthesis of cholesterol.

Lovastatin has been shown to reduce both normal and elevated LDL cholesterol concentrations. LDL is formed from VLDL and is catabolised predominantly by the high affinity LDL receptor. The mechanism of the LDL-lowering effect of lovastatin may involve both reduction of VLDL cholesterol concentration, and induction of the LDL receptor, leading to reduced production and/or increased catabolism of LDL cholesterol. Apolipoprotein B also falls substantially during treatment with lovastatin. Since each LDL particle contains one molecule of apolipoprotein B, and since little apolipoprotein B is found in other lipoproteins, this strongly suggests that lovastatin does not merely cause cholesterol to be lost from LDL, but also reduces the concentration of circulating LDL particles. In addition lovastatin can produce increases of variable magnitude in HDL cholesterol, and modestly reduces VLDL cholesterol and plasma triglycerides. The effects of lovastatin on Lp(a), fibrinogen and certain other independent biochemical risk markers for coronary heart disease are unknown.

Pharmacokinetics
Lovastatin is a lactone which is readily hydrolyzed in vivo to the corresponding β-hydroxyacid, a potent inhibitor of HMG-CoA reductase.

Following oral dose of ^{14}C-labeled lovastatin in man, 10% of the dose was excreted in urine and 83% in faeces. The latter, representing absorbed drug equivalents excreted in bile as radioactivity (lovastatin plus ^{14}C-metabolites), peaked at 2 hours and declined rapidly to about 10% of peak by 24 hours post dose. Absorption of lovastatin estimated relative to an intravenous reference dose, in each of four animal species tested was about 30% of an oral dose. In animal studies, after oral dosing lovastatin had high selectivity for the liver where it achieved substantially higher concentrations than in non-target tissues. Lovastatin undergoes extensive first-pass extraction in the liver, its primary site of action, with subsequent excretion of drug equivalents in the bile. As a consequence of extensive hepatic extraction of lovastatin, the availability of the drug to the general circulation is low and variable. In a single dose study in four hypercholesterolemic patients it was estimated that less than 5% of an oral dose of lovastatin reaches general circulation as active inhibitors. Following administration of lovastatin tablets the coefficient of variation, based on between subject variability, was approximately 40% of the AUC of total inhibitory activity in the general circulation.

Both lovastatin and its β-hydroxy acid metabolite are highly bound (>95%) to human plasma proteins. Animal studies showed that lovastatin crosses the blood-brain and placenta barriers.

The major active metabolites present in human plasma are the β-hydroxy acid of lovastatin and its 6 β-hydroxy derivative, and two additional metabolites. Peak plasma concentration of both active and total inhibitors were attached within 2 to 4 hours after administration. While the recommended therapeutic doses are 20 to 80 mg/day, linearity of inhibitory activity in general circulation was established by a single dose study employing lovastatin tablet dosages from 60 to as high as 120 mg. With a once-a day dosing regimen, plasma concentrations of total inhibitors over a dosing interval achieved a steady

state between the second and third days of dose. When lovastatin was given under fasting conditions, plasma concentrations of total inhibitors were on an average about two-thirds those found when lovastatin was administered immediately after a standard test meal.

In patients with severe renal insufficiency (creatinine clearance 10 - 30 ml/min) the plasma concentration of total inhibitors after a single dose of lovastatin was approximately two-fold higher than those in healthy volunteers.

Contraindication
The administration of lovastatin is contraindicated in patients with hypersensitivity to the drug or to any other component of the tablet. Also in patients with active liver disease or unexplained persistent elevations of serum transaminases.

Concomitant administration of strong CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors, boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin and nefazodone)

Concomitant administration of cyclosporine.

Warnings and Precautions
General: Before the initiation of treatment with MEDOSTATIN an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, weight reduction in obese patients, or to treat other underlying medical problems (such as diabetes mellitus, hypothyroidism etc.).

Liver dysfunction: During the treatment with lovastatin liver function tests should be performed. Serum transaminases, including ALT (SGPT), should be monitored before treatment begins and then every 6 weeks for the first 3 months of treatment, every 8 weeks during the remainder of first year of treatment and, after that, at 6 months intervals. Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients, measurements should be repeated promptly and then performed more frequently. If the transaminase levels show evidence of progression, particularly if they rise to 3 times the upper limit of normal and are persistent, the drug should be discontinued. The drug should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver disease or unexplained transaminase elevations are contraindications to the use of lovastatin.

Skeletal muscle: Myalgia has been associated with lovastatin therapy. Transient, mildly elevated creatinine phosphokinase levels are commonly seen in lovastatin-treated patients. However only 0.5% of patients developed myopathy (myalgia or muscle weakness associated with elevated CPK levels). Myopathy should be considered in any patient with diffused myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. Lovastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

Most of the patients who have develop myopathy (including rhabdomyolysis) while taking lovastatin, were receiving concomitant therapy with immunosuppressive drugs, gemfibrozil or lipid-lowering doses of nicotinic acid. In patients with heart transplant receiving cyclosporine concomitant with lovastatin 20 mg/day, the average plasma level of active metabolites derived from lovastatin was elevated to approximately four times the expected levels. Because of an apparent relationship between increased plasma levels of active metabolites derived from lovastatin and myopathy, the daily dosage in patients taking immunosuppressants should not exceed 20 mg/day. Even at this dosage the benefits and risks of using lovastatin in patients under immunosuppressive therapy should be carefully considered and monitored.

There have been very rare reports of an immune-mediated necrotizing myopathy (IMNM) during or after treatment with some statins. IMNM is clinically characterised by:

- Persistent proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment
- Muscle biopsy showing necrotizing myopathy without significant inflammation
- Improvement with immunosuppressive agents

Myasthenia Gravis/Ocular Myasthenia
In few cases, statins have been reported to induce de novo or aggravate pre-existing myasthenia gravis or ocular myasthenia. Medostatin should be discontinued in case of aggravation of symptoms. Recurrences when the same or a different statin was (re-) administered have been reported.

Dosage and Administration
Patient should be placed on a standard cholesterol-lowering diet before receiving lovastatin and should continue this diet during the treatment with the drug. MEDOSTATIN should be administered with meals.

Initial: The recommended starting dose is 20 mg once a day given with the evening meal. In patients with very high

cholesterol levels (> 300 mg/dl under diet) the starting dose may be 40 mg/day.
Maintenance: The recommended dosing range is 20 to 80 mg/day in single or divided doses. The maximum recommended daily dose is 80 mg. Dose should be individualized according to the patients response. Adjustments of dosage should be made at intervals of 4 weeks or more.

In patients taking immunosuppressive drugs concomitantly with lovastatin, the maximum daily administered dose is 20 mg.

Concomitant therapy:
The combined use of lovastatin with gemfibrozil should be avoided.
In patients taking danazol, verapamil, diltiazem, fibrates (except gemfibrozil) or lipid-lowering dose of niacin (≥1g/day) concomitantly with MEDOSTATIN, the dose of MEDOSTATIN should not exceed 20mg/day.

In patients staking amiodarone concomitantly with MEDOSTATIN, the dose of MEDOSTATIN should not exceed 40mg/day.

Preliminary evidence suggests that the cholesterol lowering effects of lovastatin and the bile acid sequestrant, cholestyramine, are additive.

Dosage in Renal Failure: In patients with moderate renal insufficiency there is no need for dosage adjustment, since the renal elimination of lovastatin is little. In patients with severe renal insufficiency (creatinine clearance < 30 ml/min) dosage increases above 20mg/day should be carefully considered.

Patient monitoring: During MEDOSTATIN therapy cholesterol levels should be monitored periodically. Consideration should be given to reduce the administered dose of lovastatin if cholesterol levels fall below the targeted range.

Drug Interaction
The following medications may interact with Lovastatin:

Contraindicated Drugs
Strong inhibitors of CYP3A4: Concomitant use with strong CYP3A4 inhibitors (e.g. itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors, boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin and nefazodone) is contraindicated.

Cyclosporine: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of cyclosporine. Concomitant use of this drug with lovastatin is contraindicated.

Other Drugs
- Gemfibrozil, other fibrates, niacin ≥1g/day: These drugs increase the risk of myopathy when given concomitantly with lovastatin, probably because they can produce myopathy when given alone. There is no evidence to suggest that these agents affect the pharmacokinetics of lovastatin. Myopathy, including rhabdomyolysis, has occurred in patients who were receiving coadministration of lovastatin with fibric acid derivatives or niacin.
- Danazol, verapamil, diltiazem: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of danazol, verapamil or diltiazem particularly with higher doses of lovastatin.
- Amiodarone: The risk of myopathy/rhabdomyolysis is increased when amiodarone is used concomitantly with higher doses of a closely related member of the HMG-CoA reductase inhibitor class.
- Colchicine: Cases of myopathy, including rhabdomyolysis, have been reported with lovastatin coadministered with colchicine, and caution should be exercised when prescribing lovastatin with colchicine.

Coumarin anticoagulants: Lovastatin increases moderately prothrombin time in patients receiving coumarin anticoagulants. In these patients prothrombin time should be determined before starting lovastatin and frequently enough during therapy to insure that no significant alteration of prothrombin time occurs. If the dose of lovastatin is changed the same procedure has to be repeated.

Pregnancy and Lactation
Pregnancy category: X
Safety in pregnant women has not been established. Lovastatin has been shown to produce skeletal malformations in mice and rats at plasma levels 40 times the human exposure. When the drug was administered in mice rats and rabbits at lower dosage levels (3 to 8 times the usual human doses) no malformations of the foetuses were observed. Rare reports of congenital abnormalities have been received following interuterine administration of HMG-CoA reductase inhibitors. There has been a report of severe congenital bony deformity, tracheo-esophageal fistula, and anal atresia, (Vater Association) in a baby born to a woman taking lovastatin and dexroamphetamine sulphate during the first trimester of pregnancy.

Lovastatin should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking lovastatin the drug should be discontinued and patient should be informed again of the potential hazards to the foetus.

It is not known whether lovastatin is excreted in human milk. Because there is a potential of serious adverse reactions to the nursing infant, women receiving the drug should discontinue nursing their infants.

Side Effects
Lovastatin is generally well tolerated. Adverse reactions usually are mild and transient.

The most frequent adverse reactions, occurring with a frequency of greater than 1%, are:
Gastrointestinal: Constipation, dyspepsia, flatus, abdominal pain/cramps, heartburn, nausea.
Musculoskeletal: Muscle cramps, myalgia
Nervous system/Psychiatric: Dizziness, headache
Skin: Rash/pruritus
Special senses: Blurred vision, dysgeusia

Other clinical adverse reactions reported as possibly or definitely drug-related in 0.5 to 1.0% of patients are:
Body as whole: Chest pain
Gastrointestinal: Acid regurgitation, dry mouth, vomiting
Nervous system/Psychiatric: Insomnia, paresthesia. Frequency 'not known': myasthenia gravis
Skin: Alopecia, pruritus
Special senses: Eye irritation
Musculoskeletal disorders:
Leg pain, shoulder pain, arthralgia
Frequency not known: Immune-mediated necrotizing myopathy

Concomitant therapy: When lovastatin is administered concomitantly with other lipid lowering drugs (gemfibrozil, probucol etc.) or with immunosuppresive drugs there is an increased incidence for the development of myopathy (See warnings and precautions).

The following adverse reactions have been reported with drugs of this class. Not all the effects listed below have been associated with lovastatin therapy.
Skeletal: muscle cramps, myalgia, myopathy, rhabdomyolysis, arthralgias
Neurological: Dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-occular movement, facial paresis), tremor, dizziness, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy, anxiety, insomnia, depression
Hypersensitivity reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematosus-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgea, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme including Stevens-Johnson syndrome
Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver; rarely cirrhosis, fulminant hepatic necrosis and hepatoma; anorexia vomiting
Skin: alopecia, pruritus. A variety of skin changes (e.g. nodules, discoloration, dryness of skin/mucus membranes, changes to hair/nails) have been reported
Reproductive: gynecomastia, loss of libido, erectile dysfunction
Eye: progression of cataracts (lens opacities), ophthalmoplegia. Frequency 'not known': ocular myasthenia
Laboratory abnormalities: Elevated transaminases, alkaline phosphatase, γ-glutalyl transpeptidase, and bilirubin; thyroid function abnormalities.

There have been rare post-marketing reports of cognitive impairment (e.g. memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive issues have been reported for all statins. The reports are generally non-serious and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median 3 weeks).

Increases in HbA1c and fasting blood glucose have been reported with statins. The risk of hyperglycemia, however, is outweighed by the reduction in vascular risk with statins.

Effects on the ability to drive and use machinery.
Lovastatin does not affect the ability to drive or use machinery

Overdose
Until further experience with overdose of lovastatin has been obtained, no specific treatment can be recommended. General measures for overdose should be applied and liver function should be monitored.

Five healthy male volunteers have received up to 200mg of lovastatin as a single dose without clinically significant adverse experiences. A few cases of accidental overdosage have been reported. Patients had no specific symptoms and all recovered without sequelae. The maximum dose taken was 5-6g.

It is not known if lovastatin and its metabolites can be eliminated through hemodialysis.

Storage
Store below 30°C in the original package

Shelf life
36 months
Supply
MEDOSTATIN 20mg tablets – Blister packs with 100 tablets
MEDOSTATIN 40mg tablets – Blister packs with 100 tablets

Manufacturer
Medochemie Ltd., (Central Factory), 1 – 10, Constantinoupoleos Street, Limassol 3011, Cyprus

Product Registration Holder
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