PHYSICIANS CIRCULAR

Tablets
MEVACOR®†
(lovastatin, MSD)

MEVACOR (lovastatin, MSD) is the inactive lactone form of the corresponding open hydroxyacid, which is a potent inhibitor of endogenous cholesterol synthesis, and thus is a cholesterol-lowering agent.

After gastrointestinal absorption, MEVACOR is readily hydrolyzed to the open hydroxyacid, which is a competitive inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, an enzyme which catalyzes an early and rate-limiting step in the biosynthesis of cholesterol. As a result, in clinical studies MEVACOR reduced total plasma cholesterol, low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL)-cholesterol concentrations. In addition, MEVACOR moderately increased high-density lipoprotein (HDL)-cholesterol and reduced plasma triglycerides.

The active form of lovastatin is a specific inhibitor of HMG-CoA reductase, the enzyme which catalyzes the conversion of HMG-CoA to mevalonate. Because the conversion of HMG-CoA to mevalonate is an early step in the biosynthetic pathway of cholesterol, therapy with MEVACOR would not be expected to cause an accumulation of potentially toxic sterols. In addition, HMG-CoA is also metabolized readily back to acetyl-CoA, which participates in many biosynthetic processes in the body.

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, the primary site of action, with subsequent excretion of drug in the bile.

MEVACOR has been studied in the treatment of primary hypercholesterolemia where diet alone has been insufficient. MEVACOR was highly effective in reducing total and LDL-cholesterol in heterozygous familial and non-familial forms of hypercholesterolemia, and in mixed hyperlipidemia when elevated cholesterol was cause for concern. A marked response was seen within 2 weeks, and the maximum therapeutic response occurred within 4-6 weeks. The response has been maintained during continuation of therapy. When therapy with MEVACOR is stopped, total cholesterol has been shown to return to pre-treatment levels.

MEVACOR has been shown to be effective in uncomplicated, well controlled insulin dependent (Type 1) and non-insulin dependent (Type 2) diabetic patients with primary hypercholesterolemia. Reductions of plasma lipids were comparable to that reported in non-diabetic patients. Glucose control was not adversely affected.

In clinical trials, MEVACOR, with or without concomitant therapy with colestipol, slowed the progression of coronary atherosclerosis.

INDICATIONS

- Reduction of elevated total and LDL-cholesterol levels in patients with primary hypercholesterolemia, when the response to diet and other nonpharmacological measures alone has been inadequate. MEVACOR reduces total cholesterol and LDL cholesterol, and elevates HDL cholesterol; therefore, MEVACOR lowers the ratios of total to HDL cholesterol and LDL to HDL cholesterol.

† Registered Trademark of Merck & Co., Inc., Whitehouse Station New Jersey, USA

- Reduction of elevated cholesterol levels in patients with combined hypercholesterolemia and hypertriglyceridemia, when the hypercholesterolemia is the abnormality of most concern.

- Treatment to slow the progression of coronary atherosclerosis in patients with coronary heart disease.

PEDIATRIC PATIENTS (10-17 YEARS OF AGE) WITH HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA

MEVACOR is indicated as an adjunct to diet to reduce total-C, LDL-C and apolipoprotein B levels in adolescent boys and girls who are at least one year post-menarche, 10-17 years of age, with heterozygous familial hypercholesterolemia.

DOSAGE AND ADMINISTRATION

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

HYPERCHOLESTEROLEMIA

The usual starting dose is 20 mg/day given as a single dose with the evening meal. Single daily doses given with the evening meal have been shown to be more effective than the same dose given with the morning meal, perhaps because cholesterol is synthesized mainly at night. Patients with mild to moderate hypercholesterolemia can be treated with a starting dose of 10 mg of MEVACOR. Adjustments of dosage, if required, should be made at intervals of not less than 4 weeks, to a maximum of 80 mg daily, given in single or divided doses with the morning and evening meals. Divided doses (i.e., twice daily) tend to be slightly more effective than single daily doses.

The dosage of MEVACOR should be reduced if LDL-cholesterol levels fall below 75 mg/dL (1.94 mmol/L) or total plasma cholesterol levels fall below 140 mg/dL (3.6 mmol/L).

CORONARY ATHEROSCLEROSIS

In the coronary atherosclerosis trials which utilized MEVACOR with or without concomitant therapy, the dosages used were 20 to 80 mg daily, given in single or divided doses. In the two trials which utilized MEVACOR alone, the dose was reduced if total plasma cholesterol decreased to below 110 mg/dL (2.85 mmol/L) or if LDL-cholesterol decreased to below 80 mg/dL (2.1 mmol/L), respectively.

CONCOMITANT THERAPY

MEVACOR is effective alone or in combination with bile-acid sequestrants.

In patients taking cyclosporine, danazol, gemfibrozil, other fibrates or lipid-lowering doses (≥1 g/day) of niacin concomitantly with MEVACOR, the dose of MEVACOR should not exceed 20 mg/day. In patients taking amiodarone or verapamil concomitantly with MEVACOR, the dose of MEVACOR should not exceed 40 mg/day. (See PRECAUTIONS, *Myopathy/Rhabdomyolysis* and DRUG INTERACTIONS.)

DOSAGE IN RENAL INSUFFICIENCY

Because MEVACOR does not undergo significant renal excretion, modification of dosage should not be necessary in patients with moderate renal insufficiency.

In patients with severe renal insufficiency (creatinine clearance < 30 mL/min), dosages above 20 mg/day should be carefully considered and, if deemed necessary, implemented cautiously (see PRECAUTIONS, *Myopathy/Rhabdomyolysis*).

DOSAGE IN PEDIATRIC PATIENTS (10-17 YEARS OF AGE) WITH HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA

The recommended dosing range is 10-40 mg/day; the maximum recommended dose is 40 mg/day. Doses should be individualized according to the recommended goal of therapy. Patients requiring reductions in LDL-C of 20% or more to achieve their goal should be started on 20 mg/day of MEVACOR. A starting dose of 10 mg may be considered for patients requiring smaller reductions.

CONTRAINDICATIONS

- Hypersensitivity to any component of this product.
- Active liver disease or unexplained persistent elevations of serum transaminases.
- Pregnancy and nursing (see PRECAUTIONS, PREGNANCY and NURSING MOTHERS).

PRECAUTIONS

Myopathy/Rhabdomyolysis

Lovastatin, like other inhibitors of HMG-CoA reductase, occasionally causes myopathy manifested as muscle pain, tenderness or weakness with creatine kinase (CK) above 10X the upper limit of normal (ULN). Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and rare fatalities have occurred. The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma.

- **The risk of myopathy/rhabdomyolysis is increased by concomitant use of lovastatin with the following:**

Potent inhibitors of CYP3A4 e.g., itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, or nefazodone, particularly with higher doses of lovastatin (see below; DRUG INTERACTIONS, *CYP3A4 Interactions*).

Lipid-lowering drugs that can cause myopathy when given alone: Gemfibrozil, other fibrates, or lipid-lowering doses (≥1 g/day) of niacin, particularly with higher doses of lovastatin (see below; DRUG INTERACTIONS, *Interactions with lipid-lowering drugs that can cause myopathy when given alone*).

Other drugs:

Cyclosporine or danazol particularly with higher doses of lovastatin, (see DRUG INTERACTIONS, *Other drug interactions*).

Amiodarone or Verapamil: The risk of myopathy/rhabdomyolysis is increased when either amiodarone or verapamil is used concomitantly with higher doses of a closely related member of the HMG-CoA reductase inhibitor class (see DRUG INTERACTIONS, *Other drug interactions*).

Fusidic Acid: The risk of myopathy may be increased when fusidic acid is used concomitantly with a closely related member of the HMG-CoA reductase inhibitor class (see PRECAUTIONS, *Myopathy/Rhabdomyolysis*).

- **As with other HMG-CoA reductase inhibitors, the risk of myopathy/rhabdomyolysis is dose related.** In a clinical study (EXCEL) in which patients were carefully monitored and some interacting drugs were excluded, there was one case of myopathy among 4933 patients randomized to lovastatin 20-40 mg daily for 48 weeks, and 4 among 1649 patients randomized to 80 mg daily.

Consequently:
1. Use of lovastatin concomitantly with potent CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, or nefazodone should be avoided. If treatment with itraconazole, ketoconazole, erythromycin, clarithromycin, or telithromycin is unavoidable, therapy with lovastatin should be suspended during the course of treatment. Concomitant use with other medicines labeled as having a potent inhibitory effect on CYP3A4 at therapeutic doses should be avoided unless the benefits of combined therapy outweigh the increased risk.

2. The dose of lovastatin should not exceed 20 mg daily in patients receiving concomitant medication with cyclosporine, danazol, gemfibrozil, other fibrates or lipid-lowering doses (≥1 g/day) of niacin. The combined use of lovastatin with gemfibrozil should be avoided unless the benefit of further alteration in lipid levels is likely to outweigh the increased risk of this drug combination. The benefits of the use of lovastatin in patients receiving other fibrates, niacin, cylosporine, or danazol should be carfully weighed against the risks of these drug combinations. Addition of fibrates or niacin to lovastatin typically provides little additional reduction in LDL-C, but further reductions of TG and further increases in HDL-C may be obtained. Combinations of fibrates or niacin with low doses of lovastatin have been used without myopathy in small, short-term clinical studies with careful monitoring.

3. The dose of lovastatin should not exceed 40 mg daily in patients receiving concomitant medication with amiodarone or verapamil. The combined use of lovastatin at doses higher than 40 mg daily with amiodarone or verapamil should be avoided unless the clinical benefit is likely to outweigh the increased risk of myopathy.

4. Patients on fusidic acid and lovastatin should be closely monitored. **Temporary suspension of lovastatin treatment may be considered.**

5. All patients starting therapy with lovastatin, or whose dose of lovastatin is being increased, should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, tenderness or weakness. Lovastatin therapy should be discontinued immediately if myopathy is diagnosed or suspected. The presence of these symptoms, and/or a CK level >10 times the upper limit of normal indicates myopathy. In most cases, when patients were promptly discontinued from treatment, muscle symptoms and CK increases resolved. Periodic CK determinations may be considered in patients starting therapy with lovastatin or whose dose is being increased, but there is no assurance that such monitoring will prevent myopathy.

6. Many of the patients who have developed rhabdomyolysis on therapy with lovastatin have had complicated medical histories, including renal insufficiency usually as a consequence of long-standing diabetes mellitus. Such patients merit closer monitoring. Therapy with lovastatin should be temporarily stopped a few days prior to elective major surgery and when any major medical or surgical condition supervenes.

<u>HEPATIC EFFECTS</u>

In the initial clinical trials, marked (to more than 3 times the ULN) increases in transaminases occurred in a few patients, usually appearing 3 to 12 months after the start of therapy with MEVACOR, but without the development of jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity. A liver biopsy was done in one of these patients and showed mild focal hepatitis. Some of these patients had abnormal liver function tests prior to lovastatin therapy and/or consumed substantial quantities of alcohol. In patients in whom the drug was interrupted or discontinued because of raised transaminases, including the patient who underwent liver biopsy, the transaminase levels fell slowly to pretreatment levels.

In the 48-week EXCEL study performed in 8,245 patients, the incidence of marked (more than 3 times the ULN) increases in serum transaminases on successive testing was 0.1% for placebo, 0.1% at 20 mg/day, 0.9% at 40 mg/day and 1.5% at 80 mg/day in patients on lovastatin.

It is recommended that liver function tests be performed prior to initiation of therapy in patients with a history of liver disease, or when otherwise clinically indicated. It is recommended that liver function tests be performed in all patients prior to use of 40 mg or more daily and thereafter when clinically indicated.

Should serum transaminase levels rise to more than three times the ULN, the potential risk of continuing MEVACOR should be weighed against the anticipated benefits. Transaminase measurements should be repeated promptly; if these elevations are persistent or progressive, the drug should be discontinued.

As with other lipid-lowering agents, moderate (less than three times the ULN) elevations of serum transaminases have been reported during therapy with MEVACOR (see SIDE EFFECTS). These changes appeared soon after initiation of therapy with MEVACOR, were usually transient, and were not accompanied by any symptoms; interruption of treatment was not required.

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 persistent elevations of serum transaminases is a contraindication to the use of MEVACOR (see CONTRAINDICATIONS).

OPHTHALMIC EVALUATIONS

In the absence of any drug therapy, an increase in the prevalence of lens opacities with time is expected as a result of aging. Long term data from clinical trials do not indicate an adverse effect of lovastatin on the human lens.

PREGNANCY

MEVACOR is contraindicated during pregnancy.

Safety in pregnant women has not been established. No controlled clinical trials with lovastatin have been conducted in pregnant women. Rare reports of congenital anomalies following intrauterine exposure to HMG-CoA reductase inhibitors have been received. However, in an analysis of approximately 200 prospectively followed pregnancies exposed during the first trimester to MEVACOR or another closely related HMG-CoA reductase inhibitor, the incidence of congenital anomalies was comparable to that seen in the general population. This number of pregnancies was statistically sufficient to exclude a 2.5-fold or greater increase in congenital anomalies over the background incidence.

Although there is no evidence that the incidence of congenital anomalies in offspring of patients taking MEVACOR or another closely related HMG-CoA reductase inhibitor differs from that observed in the general population, maternal treatment with MEVACOR may reduce the fetal levels of mevalonate which is a precursor of cholesterol biosynthesis. Atherosclerosis is a chronic process, and ordinarily discontinuation of lipid-lowering drugs during pregnancy should have little impact on the long-term risk associated with primary hypercholesterolemia. For these reasons, MEVACOR should not be used in women who are pregnant, trying to become pregnant or suspect they are pregnant. Treatment with MEVACOR should be suspended for the duration of pregnancy or until it has been determined that the woman is not pregnant. (See CONTRAINDICATIONS.)

NURSING MOTHERS

It is not known whether MEVACOR is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious side effects, women taking MEVACOR should not nurse their infants (see CONTRAINDICATIONS).

PEDIATRIC USE

Safety and effectiveness of lovastatin in patients 10-17 years of age with heterozygous familial hypercholesterolemia have been evaluated in controlled clinical trials of 48 weeks duration in adolescent boys and controlled clinical trials of 24 weeks duration in girls who were at least one year post-menarche.

Patients treated with lovastatin had an adverse experience profile generally similar to that of patients treated with placebo. **Doses greater than 40 mg have not been studied in this population**. In these limited controlled studies, there was no detectable effect on growth or sexual maturation in the adolescent boys or on menstrual cycle length in girls. (See DOSAGE AND ADMINISTRATION, SIDE EFFECTS.) Adolescent females should be counseled on appropriate contraceptive methods while on lovastatin therapy (see CONTRAINDICATIONS and PRECAUTIONS, PREGNANCY). Lovastatin has not been studied in pre-pubertal patients or patients younger than 10 years of age.

ELDERLY

In one controlled study in elderly patients over the age of 60, efficacy appeared similar to that seen in the population as a whole, and there was no apparent increase in the frequency of clinical or laboratory adverse findings.

HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA

In patients with the rare homozygous familial hypercholesterolemia, MEVACOR was less effective, possibly because these patients have no functional LDL receptors. MEVACOR appears to be more likely to raise serum transaminases (see SIDE EFFECTS) in these homozygous patients.

HYPERTRIGLYCERIDEMIA

MEVACOR has only a moderate triglyceride-lowering effect and it is not indicated where hypertriglyceridemia is the abnormality of most concern (i.e., hyperlipidemia types I, IV and V).

DRUG INTERACTIONS

CYP3A4 Interactions
Lovastatin is metabolized by CYP3A4 but has no CYP3A4 inhibitory activity; therefore it is not expected to affect the plasma concentrations of other drugs metabolized by CYP3A4. Potent inhibitors of CYP3A4 (below) increase the risk of myopathy by reducing the elimination of lovastatin.

See PRECAUTIONS, *Myopathy/Rhabdomyolysis*.
Itraconazole
Ketoconazole
Erythromycin
Clarithromycin
Telithromycin
HIV protease inhibitors
Nefazodone

Interactions with lipid-lowering drugs that can cause myopathy when given alone
The risk of myopathy is also increased by the following lipid-lowering drugs that are not potent inhibitors of CYP3A4, but which can cause myopathy when given alone.

See PRECAUTIONS, *Myopathy/Rhabdomyolysis.*
Gemfibrozil
Other fibrates
Niacin (nicotinic acid) (≥1 g/day)

Other drug interactions
Cyclosporine or Danazol: The risk of myopathy/rhabdomyolysis is increased by concomitant administration or danazol particularly with higher doses of lovastatin (see PRECAUTIONS, *Myopathy/Rhabdomyolysis*).

Amiodarone or Verapamil: The risk of myopathy/rhabdomyolysis is increased when either amiodarone or verapamil is used concomitantly with higher doses of a closely related member of the HMG-CoA reductase inhibitor class (see PRECAUTIONS, *Myopathy/Rhabdomyolysis*).

Fusidic Acid: The risk of myopathy may be increased when fusidic acid is used concomitantly with a closely related member of the HMG-CoA reductase inhibitor class (see PRECAUTIONS, *Myopathy/Rhabdomyolysis*; CLINICAL PHARMACOLOGY, PHARMACOKINETICS).

Other interactions
Grapefruit juice contains one or more components that inhibit CYP3A4 and can increase the plasma levels of drugs metabolized by CYP3A4. The effect of typical consumption (one 250-ml glass daily) is minimal (34% increase in active plasma HMG-CoA reductase inhibitory activity as measured by the area under the concentration-time curve) and of no clinical relevance. However, very large quantities (over 1 liter daily) significantly increase the plasma level of HMG-CoA reductase inhibitory activity during lovastatin therapy and should be avoided (see PRECAUTIONS, *Myopathy/Rhabdomyolysis*).

COUMARIN DERIVATIVES

When lovastatin and coumarin anticoagulants are administered concomitantly, prothrombin time may be increased in some patients. It is recommended that in patients taking anticoagulants, prothrombin time be determined before starting lovastatin and frequently enough during early therapy to ensure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at intervals usually recommended for patients on coumarin anticoagulants. If the dose of lovastatin is changed, the same procedure should be repeated. Lovastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

SIDE EFFECTS

MEVACOR is generally well-tolerated; for the most part side effects have been mild and transient in nature.

In controlled clinical studies, side effects (considered possibly, probably or definitely drug related) occurring with a frequency of greater than 1% were: flatulence, diarrhea, constipation, nausea, dyspepsia, dizziness, blurred vision, headache, muscle cramps, myalgia, rashes, and abdominal pain. Patients receiving active control agents had a similar or higher incidence of gastrointestinal side effects. Other side effects occurring in 0.5 to 1.0 % of patients were: fatigue, pruritus, dry mouth, insomnia, sleep disorders, and dysgeusia.

Myopathy and rhabdomyolysis have been reported rarely.

In the 48-week expanded clinical evaluation of lovastatin (EXCEL study) comparing lovastatin to placebo, the adverse experiences reported were similar to those of the initial studies, and the incidence on drug and placebo was not statistically different.

The following additional side effects have been reported since the drug was marketed: hepatitis, cholestatic jaundice, vomiting, anorexia, paresthesia, peripheral neuropathy, psychic disturbances including anxiety, alopecia, toxic epidermal necrolysis and erythema multiforme, including Stevens - Johnson syndrome.

An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, thrombocytopenia, leukopenia, eosinophilia, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, flushing, chills, dyspnea and malaise.

LABORATORY TEST FINDINGS

Marked and persistent increases of serum transaminases have been reported rarely (see PRECAUTIONS). Other liver function test abnormalities including elevated alkaline phosphatase and bilirubin have been reported. Increases in serum CK levels (attributable to the noncardiac fraction of CK) have been reported. These have usually been mild and transient, marked elevations have been reported rarely (see PRECAUTIONS, *Myopathy/Rhabdomyolysis*).

PEDIATRIC PATIENTS (AGES 10-17 YEARS)

In a 48-week controlled study in adolescent boys with heterozygous familial hypercholesterolemia (n=132) and a 24-week controlled study in girls who were at least 1 year post-menarche with heterozygous familial hypercholesterolemia (n=54), the safety and tolerability profile of the groups treated with MEVACOR (10 to 40 mg daily) was generally similar to that of the groups treated with placebo (see PRECAUTIONS, PEDIATRIC USE).

OVERDOSAGE

Until further experience is obtained no specific treatment of overdosage with MEVACOR can be recommended. General measures should be adopted, and liver function should be monitored.

The dialyzability of lovastatin and its metabolites in man is not known at present.

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

AVAILABILITY

Tablet MEVACOR® is supplied in blister strip of 10 tablets 1 X 10's. Each tablet contains lovastatin MSD equivalent to 20 mg lovastatin.

STORAGE

Protect from light and store in a well-closed, light-resistant container.

Store below 30°C (86°F).