PDR 1997

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atitis B and other infectious agents from one person to another.

10 Dose Vial (available only to government agencies/institutions)—Withdraw the entire contents (7 mL) of the diluent vial into the sterile syringe to be used for reconstitution, and introduce into the 10 dose vial of lyophilized vaccine. Agitate to ensure thorough mixing. The outer labeling suggests "For Jet Injector or Syringe Use". Use with separate sterile syringes is permitted for containers of 10 doses or less. The vaccine and diluent do not contain preservatives; therefore, the user must recognize the potential contamination hazards and exercise special precautions to protect the sterility and potency of the product. The use of aseptic techniques and proper storage prior to and after restoration of the vaccine and subsequent withdrawal of the individual doses is essential. Use 0.5 mL of the reconstituted vaccine for subcutaneous injection.

It is important to use a separate sterile syringe and needle for each individual patient to prevent transmission of hepatitis B and other infectious agents from one person to another.

50 Dose Vial (available only to government agencies/institutions)—Withdraw the entire contents (30 mL) of diluent vial into the sterile syringe to be used for reconstitution and introduce into the 50 dose vial of lyophilized vaccine. Agitate to ensure thorough mixing. With full aseptic precautions, attach the vial to the sterilized multidose jet injector apparatus. Use 0.5 mL of the reconstituted vaccine for subcutaneous injection.

Each dose contains not less than the equivalent of 1,000 $TCID_{50}$ of the U.S. Reference Rubella Virus.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

MERUVAX II, when reconstituted, is clear yellow.

HOW SUPPLIED

No. 4747—MERUVAX II is supplied as a single-dose vial of lyophilized vaccine,
NDC 0006-4747-00, and a vial of diluent.

No. 4673/4309—MERUVAX II is supplied as follows: (1) a box of 10 single-dose vials of lyophilized vaccine (package A), **NDC** 0006-4673-00; and (2) a box of 10 vials of diluent (package B). To conserve refrigerator space, the diluent may be stored separately at room temperature.
(6505-00-145-0180, Ten Pack).

Available only to government agencies/institutions:

No. 4674—MERUVAX II is supplied as one 10 dose vial of lyophilized vaccine,
NDC 0006-4674-00, and one 7 mL vial of diluent.

No. 4675—MERUVAX II is supplied as one 50 dose vial of lyophilized vaccine,
NDC 0006-4675-00, and one 30 mL vial of diluent.
(6505-01-222-6468; 50 Dose).

Storage

It is recommended that the vaccine be used as soon as possible after reconstitution. Protect vaccine from light at all times, since such exposure may inactivate the virus. Store reconstituted vaccine in the vaccine vial in a dark place at 2–8°C (36–46°F) and discard if not used within 8 hours.

A.H.F.S. Category: 80:12
7680317 Issued March 1995

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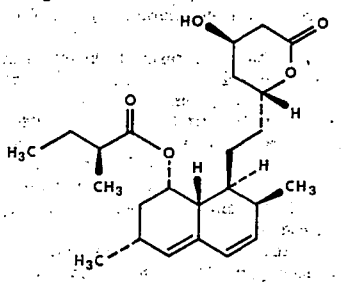
MEVACOR® Tablets
(Lovastatin), U.S.P.

DESCRIPTION

MEVACOR* (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-hydroxyacid 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 is [1*S*-[1α(*R* *),3α,7β,8β(2*S* *,4*S* *),8aβ]]-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-2-yl)ethyl]-1-naphthalenyl 2-methylbutanoate. The empirical formula of lovastatin is $C_{24}H_{36}O_5$ and its molecular weight is 404.55. Its structural formula is:



Lovastatin is a white, nonhygroscopic crystalline powder that is insoluble in water and sparingly soluble in ethanol, methanol, and acetonitrile.

Tablets MEVACOR are supplied as 10 mg, 20 mg and 40 mg tablets for oral administration. In addition to the active ingredient lovastatin, each tablet contains the following inactive ingredients: cellulose, lactose, magnesium stearate, and starch. Butylated hydroxyanisole (BHA) is added as a preservative. Tablets MEVACOR 10 mg also contain red ferric oxide and yellow ferric oxide. Tablets MEVACOR 20 mg also contain FD&C Blue 2. Tablets MEVACOR 40 mg also contain D&C Yellow 10 and FD&C Blue 2.

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CLINICAL PHARMACOLOGY

The involvement of low-density lipoprotein (LDL) cholesterol in atherogenesis has been well-documented in clinical and pathological studies, as well as in many animal experiments. Epidemiological studies have established that high LDL (low-density lipoprotein) cholesterol and low HDL (high-density lipoprotein) cholesterol are both risk factors for coronary heart disease. The Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT), coordinated by the National Institutes of Health (NIH) studied men aged 35–59 with total cholesterol levels 265 mg/dL (6.8 mmol/L) or greater, LDL cholesterol values 175 mg/dL (4.5 mmol/L) or greater and triglyceride levels not more than 300 mg/dL (3.4 mmol/L). This seven-year, double-blind, placebo-controlled study demonstrated that lowering LDL cholesterol with diet and cholestyramine decreased the combined rate of coronary heart disease death plus non-fatal myocardial infarction.

MEVACOR has been shown to reduce both normal and elevated LDL cholesterol concentrations. LDL is formed from VLDL and is catabolized predominantly by the high affinity LDL receptor. The mechanism of the LDL-lowering effect of MEVACOR 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 MEVACOR. Since each LDL particle contains one molecule of apolipoprotein B, and since little apolipoprotein B is found in other lipoproteins, this strongly suggests that MEVACOR does not merely cause cholesterol to be lost from LDL, but also reduces the concentration of circulating LDL particles. In addition, MEVACOR can produce increases of variable magnitude in HDL cholesterol, and modestly reduces VLDL cholesterol and plasma triglycerides (see Tables I–IV under *Clinical Studies*). The effects of MEVACOR on Lp(a), fibrinogen, and certain other independent biochemical risk markers for coronary heart disease are unknown.

MEVACOR is a specific inhibitor of HMG-CoA reductase, the enzyme which catalyzes the conversion of HMG-CoA to mevalonate. The conversion of HMG-CoA to mevalonate is an early step in the biosynthetic pathway for cholesterol.

Pharmacokinetics

Lovastatin is a lac
the corresponding
HMG-CoA reductase
the basis for an assa
hydroxyacid metabo
base hydrolysis, act
tors) in plasma follo
Following an oral dos
of the dose was exc
represents absorbed
well as any unabsorbe
radioactivity (lovast
hours and declined
postdose. Absorption
intravenous reference
tested, averaged abou
ies, after oral dosing,
liver, where it achieve
than in non-target tis
first-pass extraction
with subsequent excre
a consequence of exten
the availability of drug
variable. In a single do
patients, it was estimate
lovastatin reaches the
tors. Following admini
ficient of variation, ba
was approximately 40%
of total inhibitory activi
Both lovastatin and its
bound (> 95%) to huma
demonstrated that lov
placental barriers.
The major active metabo
the β-hydroxyacid of lo
and two additional metab
of both active and total in
hours of dose administra
peutic dose range is 10
activity in the general circ
dose study employing lova
high as 120 mg. With a
concentrations of total in
achieved a steady state be
therapy and were about
dose. When lovastatin wa
plasma concentrations di
about two-thirds those fou
tered immediately after
In a study of patients with
nine clearance 10–30 mL/
total inhibitors after a sing
mately two-fold higher than

Clinical Studies

MEVACOR has been show
ing total and LDL choleste
non-familial forms of prim
mixed hyperlipidemia. A
weeks, and the maximum
within 4–6 weeks. The respo
tinuation of therapy. Single
were more effective than th
ing, perhaps because chole
night.

In multicenter, double-blind
or non-familial hypercholest
tered in doses ranging from 10
compared to placebo. MEVA
cantly decreased total plasm
cholesterol (LDL-C), total ch
TAL-C/HDL-C) ratio and LD
(LDL-C/HDL-C) ratio. In
increases of variable magnitu
and modestly decreased VLD
plasma triglycerides (TRIG)
dose response results).
The results of a study in patie
terolemia are presented in Ta
[See table below.]
MEVACOR was compared
ized open parallel study and
parallel study. Both studies
with hypercholesterolemia wh
dial infarction. Summary resu
studies are presented in Tabl
[See tables at top of next page
MEVACOR was studied in con
terolemic patients with well-
dent diabetes mellitus with no
of MEVACOR on lipids and lip
file of MEVACOR were similar
ies in nondiabetics. MEVACOR
effect on glycemic control or on
hypoglycemic agents.

TABLE I
MEVACOR vs Placebo
(Mean Percent Change from Baseline After 6 Weeks)

DOSAGE	N	TOTAL-C	LDL-C	HDL-C	LDL-C/HDL-C	TOTAL-C/HDL/C	TRIG.
Placebo	33	−2	−1	−1	0	+1	+9
MEVACOR							
10 mg q.p.m.	33	−16	−21	+5	−24	−19	−10
20 mg q.p.m.	33	−19	−27	+6	−30	−23	+9
10 mg b.i.d.	32	−19	−28	+8	−33	−25	−7
40 mg q.p.m.	33	−22	−31	+5	−33	−25	−8
20 mg b.i.d.	36	−24	−32	+2	−32	−24	−6

TABLE II
MEVACOR vs. Cholestyramine
(Percent Change from Baseline After 12 Weeks)

TOTAL-C (mean)	LDL-C (mean)	HDL-C (mean)	LDL-C/ HDL-C (mean)	TOTAL-C/ HDL-C (mean)	VLDL-C (median)	TRIG. (median)
[illegible]	−32	+9	−36	−31	−34	−21
[illegible]	−42	+8	−44	−37	−31	−27
[illegible]	−23	+8	−27	−21	+2	+11

TABLE III
MEVACOR vs. Probucol
(Percent Change from Baseline After 14 Weeks)

TOTAL-C (mean)	LDL-C (mean)	HDL-C (mean)	LDL-C/ HDL-C (mean)	TOTAL-C/ HDL-C (mean)	VLDL-C (median)	TRIG. (median)
[illegible]	−32	+9	−38	−31	−37	−18
[illegible]	−37	+11	−42	−36	−27	−17
[illegible]	−40	+12	−45	−39	−40	−25
[illegible]	−8	−23	+26	+23	−13	+1

TABLE IV
MEVACOR vs. Placebo
(Percent Change from Baseline—
Average Values Between Weeks 12 and 48)

TOTAL-C (mean)	LDL-C (mean)	HDL-C (mean)	LDL-C/ HDL-C (mean)	TOTAL-C/ HDL-C (mean)	TRIG. (median)
+0.7	+0.4	+2.0	+0.2	+0.6	+4
−17	−24	+6.6	−27	−21	−10
−22	−30	+7.2	−34	−26	−14
−24	−34	+8.6	−38	−29	−16
−29	−40	+9.5	−44	−34	−19

...Lovastatin (EXCEL) Study
...placebo in 8,245 patients with
...cholesterol 240–300 mg/dL [6.2
...cholesterol >160 mg/dL [4.1
...double-blind, parallel, 48-week
...the lipid measurements (Table
...patients were dose-related and
...placebo (p ≤0.001). These
...out the study.

...Atherosclerosis Intervention
...therapy with lovastatin on coro-
...ed by coronary angiography
...this randomized, double-blind,
...were treated with conven-
...and 325 mg of aspirin every
...in 20–80 mg daily or placebo.
...baseline and at two years by
...coronary angiography (QCA).
...the progression of lesions as
...per-patient in minimum lu-
...endpoint) and percent diameter
...proportions of patients catego-
...(33% vs. 50%) and with new

...the Monitored Atherosclerosis
...patients were treated with diet
...ly or placebo. No statistically
...lovastatin and placebo was
...(mean change per patient in
...all lesions), or for most secon-
...assessment by angiographers
...opinion of overall angiographic
...was also a secondary endpoint.
...slowing of disease was seen,
...patients treated with lovastatin
...patients.
...Treatment Study (FATS),
...combination with a bile acid
...hyperlipidemic subjects signifi-
...of progression and increased
...of coronary atherosclerotic
...and, in some cases, low-dose

...progression of atherosclerosis
...been corroborated by similar
...re. In the Asymptomatic Ca-
...y (ACAPS), the effect of ther-
...atherosclerosis was assessed
...in hyperlipidemic patients with
...out known coronary heart dis-
...double-blind, controlled clinical
...omized in a 2 x 2 factorial design
...mg daily and/or warfarin. Ul-
...walls were used to determine the

change per patient from baseline to three years in mean maximum intimal-medial thickness (IMT) of 12 measured segments. There was a significant regression of carotid lesions in patients receiving lovastatin alone compared to those receiving placebo alone (p=0.001). The predictive value of changes in IMT for stroke has not yet been established. In the lovastatin group there was a significant reduction in the number of patients with major cardiovascular events relative to the placebo group (5 vs. 14) and a significant reduction in all-cause mortality (1 vs. 8).

Eye

There was a high prevalence of baseline lenticular opacities in the patient population included in the early clinical trials with lovastatin. During these trials the appearance of new opacities was noted in both the lovastatin and placebo groups. There was no clinically significant change in visual acuity in the patients who had new opacities reported nor was any patient, including those with opacities noted at baseline, discontinued from therapy because of a decrease in visual acuity.

A three-year, double-blind, placebo-controlled study in hypercholesterolemic patients to assess the effect of lovastatin on the human lens demonstrated that there were no clinically or statistically significant differences between the lovastatin and placebo groups in the incidence, type or progression of lenticular opacities. There are no controlled clinical data assessing the lens available for treatment beyond three years.

INDICATIONS AND USAGE

Therapy with lipid-altering agents should be a component of multiple risk factor intervention in those individuals at significantly increased risk for artherosclerotic vascular disease due to hypercholesterolemia. MEVACOR is indicated as an adjunct to diet for the reduction of elevated total and LDL cholesterol levels in patients with primary hypercholesterolemia (Types IIa and IIb***), when the response to diet restricted in saturated fat and cholesterol and to other nonpharmacological measures alone has been inadequate.

MEVACOR is also indicated to slow the progression of coronary atherosclerosis in patients with coronary heart disease as part of a treatment strategy to lower total and LDL cholesterol to target levels. Most subjects in the angiographic studies were middle-aged men; therefore, it is not clear to what extent these data can be extrapolated to women and the elderly (see CLINICAL PHARMACOLOGY, *Clinical Studies*).

Prior to initiating therapy with lovastatin, secondary causes for hypercholesterolemia (e.g., poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy, alcoholism) should be excluded, and a lipid profile performed to measure TOTAL-C, HDL-C, and triglycerides (TG). For patients with TG less than 400 mg/dL (<4.5 mmol/L), LDL-C can be estimated using the following equation:

LDL-C = Total cholesterol − [0.2 × (triglycerides) + HDL-C]

For TG levels >400 mg/dL (>4.5 mmol/L), this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation. In hypertriglyceridemic patients, LDL-C may be low or normal despite elevated TOTAL-C. In such cases, MEVACOR is not indicated.

The National Chotlesterol Education Program (NCEP) Treatment Guidelines are summarized below:

Definite Atherosclerotic Disease†	Two or More Other Risk Factors††	LDL-Cholesterol mg/dL (mmol/L) Initiation Level	Goal
NO	NO	≥190 (≥4.9)	<160 (<4.1)
NO	YES	≥160 (≥4.1)	<130 (<3.4)
YES	YES or NO	≥130 (≥3.4)	≤100 (≤2.6)

† Coronary heart disease or peripheral vascular disease (including symptomatic carotid artery disease).

†† Other risk factors for coronary heart disease (CHD) include: age (males: ≥45 years; females: ≥55 years of premature menopause without estrogen replacement therapy); family history of premature CHD; current cigarette smoking; hypertension; confirmed HDL-C <35 mg/dL (<0.91 mmol/L); and diabetes mellitus. Subtract one risk factor if HDL-C is ≥60 mg/dL (≥1.6 mmol/L).

Since the goal of treatment is to lower LDL-C, the NCEP recommends that LDL-C levels be used to initiate and assess treatment response. Only if LDL-C levels are not available, should the TOTAL-C be used to monitor therapy.

Although MEVACOR may be useful to reduce elevated LDL cholesterol levels in patients with combined hypercholesterolemia and hypertriglyceridemia where hypercholesterolemia is the major abnormality (Type IIb hyperlipoproteinemia), it has not been studied in conditions where the major abnormality is elevation of chylomicrons, VLDL or IDL (i.e., hyperlipoproteinemia types I, III, IV, or V).***

***Classification of Hyperlipoproteinemias

Type	Lipoproteins elevated	Lipid Elevations major	minor
I (rare)	chylomicrons	TG	→C
IIa	LDL	C	—
IIb	LDL, VLDL	C	TG
III (rare)	IDL	C/TG	—
IV	VLDL	TG	→C
V (rare)	chylomicrons, VLDL	TG	→C

C = cholesterol, TG = triglycerides,
LDL = low-density lipoprotein,
VLDL = very low-density lipoprotein,
IDL = intermediate-density lipoprotein.

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.
Active liver disease or unexplained persistent elevations of serum transaminases (see WARNINGS).

Pregnancy and lactation. Atherosclerosis is a chronic process and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Moreoever, cholesterol and other products of the cholesterol biosynthesis pathway are essential components for fetal development, including synthesis of steroids and cell membranes. Because of the ability of inhibitors of HMG-CoA reductase such as MEVACOR to decrease the synthesis of cholesterol and possibly other products of the cholesterol biosynthesis pathway, MEVACOR may cause fetal harm when administered to a pregnant woman. Therefore, lovastatin is contraindicated during pregnancy. **Lovastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive.** If the patient becomes pregnant while taking this drug, lovastatin should be discontinued and the patient should be apprised of the potential hazard to the fetus.

WARNINGS

Liver Dysfunction

Marked persistent increases (to more than 3 times the upper limit of normal) in serum transaminases occurred in 1.9% of

Continued on next page

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adult patients who received lovastatin for at least one year in early clinical trials (see ADVERSE REACTIONS). When the drug was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pretreatment levels. The increases usually appeared 3 to 12 months after the start of therapy with lovastatin, and were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity. In the EXCEL study (see CLINICAL PHARMACOLOGY, *Clinical Studies*), the incidence of marked persistent increases in serum transaminases over 48 weeks 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. However, in post-marketing experience with MEVACOR, symptomatic liver disease has been reported rarely at all dosages (see ADVERSE REACTIONS).

It is recommended that liver function tests be performed before the initiation of treatment, at 6 and 12 weeks after initiation of therapy or elevation of dose, and periodically thereafter (e.g., semiannually). Patients who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding and be followed thereafter with frequent liver function tests until the abnormality(ies) return to normal. Should an increase in AST or ALT of three times the upper limit of normal or greater persist, withdrawal of therapy with MEVACOR is recommended.

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.

As with other lipid-lowering agents, moderate (less than three times the upper limit of normal) elevations of serum transaminases have been reported following therapy with MEVACOR (see ADVERSE REACTIONS). These changes appeared soon after initiation of therapy with MEVACOR, were often transient, were not accompanied by any symptoms and interruption of treatment was not required.

Skeletal Muscle

Rhabdomyolysis has been associated with lovastatin therapy alone, when combined with immunosuppressive therapy including cyclosporine in cardiac transplant patients, and when combined in non-transplant patients with either gemfibrozil or lipid-lowering doses (≥ 1 g/day) of nicotinic acid. Some of the affected patients had pre-existing renal insufficiency, usually as a consequence of long-standing diabetes. Acute renal failure from rhabdomyolysis has been seen more commonly with the lovastatin-gemfibrozil combination, and has also been reported in transplant patients receiving lovastatin plus cyclosporine.

Rhabdomyolysis with renal failure has been reported in a renal transplant patient receiving cyclosporine and lovastatin shortly after a dose increase in the systemic antifungal agent itraconazole. Another transplant patient on cyclosporine and a different HMG-CoA reductase inhibitor experienced muscle weakness accompanied by marked elevation of creatine phosphokinase following the initiation of systemic itraconazole therapy. The HMG-CoA reductase inhibitors and the azole derivative antifungal agents inhibit cholesterol biosynthesis at different points in the biosynthetic pathway. In patients receiving cyclosporine, lovastatin should be temporarily discontinued if systemic azole derivative antifungal therapy is required; patients not taking cyclosporine should be carefully monitored if systemic azole derivative antifungal therapy is required.

Rhabdomyolysis with or without renal impairment has been reported in seriously ill patients receiving erythromycin concomitantly with lovastatin. Therefore, patients receiving concomitant lovastatin and erythromycin should be carefully monitored.

Fulminant rhabdomyolysis has been seen as early as three weeks after initiation of combined therapy with gemfibrozil and lovastatin, but may be seen after several months. For these reasons, it is felt that, in most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefits of combined therapy with lovastatin and gemfibrozil do not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. While it is not known whether this interaction occurs with fibrates other than gemfibrozil, myopathy and rhabdomyolysis have occasionally been associated with the use of other fibrates alone, including clofibrate. Therefore, the combined use of lovastatin with other fibrates should generally be avoided.

Physicians contemplating combined therapy with lovastatin and lipid-lowering doses of nicotinic acid or with immunosuppressive drugs should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic CPK determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy. The monitoring of lovastatin drug and metabolite levels may be considered in transplant patients who are treated with immunosuppressives and lovastatin.

Lovastatin therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis, including: severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures.

Myalgia has been associated with lovastatin therapy. Transient, mildly elevated creatine phosphokinase levels are commonly seen in lovastatin-treated patients. However, in early clinical trials, approximately 0.5% of patients developed a myopathy, i.e., myalgia or muscle weakness associated with markedly elevated CPK levels. In the EXCEL study (see CLINICAL PHARMACOLOGY, *Clinical Studies*), five (0.1%) patients taking lovastatin alone (one at 40 mg q.p.m., and four at 40 mg b.i.d.) developed myopathy (muscle symptoms and CPK levels > 10 times the upper limit of normal). Myopathy should be considered in any patient with diffuse 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 developed myopathy (including rhabdomyolysis) were taking lovastatin concomitantly with immunosuppressive drugs, gemfibrozil, or lipid-lowering doses of nicotinic acid. In initial clinical trials, about 30 percent of patients on concomitant immunosuppressive therapy including cyclosporine developed myopathy. Most of these patients were receiving lovastatin at doses of 40 to 80 mg/day. In reports from 7 subsequent studies, 148 cyclosporine-treated patients (105 cardiac and 43 renal) received concurrent lovastatin doses of 10 to 60 mg/day (the majority receiving 20 mg/day) for mean periods of 3 to 15 months. There was one case of rhabdomyolysis (0.6%) and one case of significant CPK elevation. In earlier studies of patients taking lovastatin in combination with gemfibrozil or niacin, the incidences of myopathy were approximately 5% and 2%, respectively.

In six patients with cardiac transplants taking immunosuppressive therapy including cyclosporine concomitantly 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 (see DOSAGE AND ADMINISTRATION). Even at this dosage, the benefits and risks of using lovastatin in patients taking immunosuppressants should be carefully considered.

PRECAUTIONS

General

Before instituting therapy with MEVACOR, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, weight reduction in obese patients, and to treat other underlying medical problems (see INDICATIONS AND USAGE).

Lovastatin may elevate creatine phosphokinase and transaminase levels (see WARNINGS and ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with lovastatin.

Homozygous Familial Hypercholesterolemia

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

Information for Patients

Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

Drug Interactions

Immunosuppressive Drugs, Itraconazole, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin: See WARNINGS, *Skeletal Muscle.*

Coumarin Anticoagulants: In a small clinical trial in which lovastatin was administered to warfarin treated patients, no effect on prothrombin time was detected. However, another HMG-CoA reductase inhibitor has been found to produce a less than two seconds increase in prothrombin time in healthy volunteers receiving low doses of warfarin. Also, bleeding and/or increased prothrombin time have been reported in a few patients taking coumarin anticoagulants concomitantly with lovastatin. It is recommended that in patients taking anticoagulan[illegible] mined before starting lovasta[illegible] ing early therapy to insure th[illegible] prothrombin time occurs. On[illegible] has been documented, proth[illegible] at the intervals usually recom[illegible] rin anticoagulants. If the do[illegible] same procedure should be rep[illegible] not been associated with bleed[illegible] thrombin time in patients not[illegible]

Antipyrine: Because lovasta[illegible] macokinetics of antipyrine or [illegible] other drugs metabolized via th[illegible] are not expected.

Propranolol: In normal volun[illegible] significant pharmacokinetic [illegible] tion with concomitant admini[illegible] statin and propranolol.

Digoxin: In patients with hy[illegible] tant administration of lovastati[illegible] effect on digoxin plasma con[illegible]

Oral Hypoglycemic Agents: [illegible] MEVACOR in hypercholestero[illegible] diabetic patients, there was no [illegible] zide or with chlorpropamide (se[illegible] OGY, *Clinical Studies*).

Other Concomitant Therapy: [illegible] studies were not performed, [illegible] was used concomitantly with be[illegible] blockers, diuretics and nons[illegible] drugs (NSAIDs) without evide[illegible] adverse interactions.

Endocrine Function

HMG-CoA reductase inhibitor[illegible] synthesis and as such might the[illegible] or gonadal steroid productions [illegible] drugs in this class have been [illegible] drug effects on basal and res[illegible] clinical studies have shown th[illegible] basal plasma cortisol concent[illegible] serve, and does not reduce basal [illegible] tration. Another HMG-CoA [illegible] shown to reduce the plasma tes[illegible] the same study, the mean tes[illegible] slightly but not significantly [illegible] lovastatin 40 mg daily for 16 we[illegible] HMG-CoA reductase inhibitors [illegible] been studied in adequate numb[illegible] fects, if any, on the pituitary-go[illegible] women are unknown. Patients [illegible] develop clinical evidence of end[illegible] evaluated appropriately. Caution [illegible] an HMG-CoA reductase inhibito[illegible] lower cholesterol levels is admin[illegible] ceiving other drugs (e.g., [illegible] cimetidine) that may decrease the[illegible] enous steroid hormones.

CNS Toxicity

Lovastatin produced optic nerv[illegible] degeneration of retinogeniculate [illegible] dogs in a dose-dependent fashion [illegible] dose that produced mean plasma [illegible] higher than the mean drug level [illegible] est recommended dose (as measu[illegible] tory activity). Vestibulocochlear [illegible] tion and retinal ganglion cell chan[illegible] dogs treated for 14 weeks at 180 [illegible] resulted in a mean plasma drug [illegible] seen with the 60 mg/kg/day do[illegible] CNS vascular lesions, characteri[illegible] rhage and edema, mononuclear [illegible] lar spaces, perivascular fibrin de[illegible] vessels, were seen in dogs treated [illegible] 180 mg/kg/day, a dose which pr[illegible] (C_{max}) which were about 30 tim[illegible] values in humans taking 80 mg/[illegible] Similar optic nerve and CNS [illegible] observed with other drugs of th[illegible] Cataracts were seen in dogs trea[illegible] 180 mg/kg/day and 1 year at 60 [illegible]

Carcinogenesis, Mutagenesis, Impa[illegible]

In a 21-month carcinogenic study [illegible] tically significant increase in the [illegible] carcinomas and adenomas in bo[illegible] mg/kg/day. This dose produced [illegible] sure 3 to 4 times that of human [illegible] mended dose of lovastatin (drug [illegible] total HMG-CoA reductase inhib[illegible] plasma). Tumor increases were no[illegible] kg/day, doses that produced drug [illegible] that of humans at the 80 mg/day d[illegible] cant increase in pulmonary aden[illegible] mice at approximately 4 times [illegible] (Although mice were given 300 tim[illegible] on a mg/kg body weight basis, pl[illegible]

higher in mice than in

papilloma in the non- mice beginning at expo- The glandular mucosa h contains only glandu-

in rats, there was a posi- hepatocellular carcinoge- between 2–7 times that of in rats were 5, 30 and

neoplasms in rats appears with other HMG-CoA

was administered to 400 mg/kg body weight, levels approximately 3, human serum drug activity) after a 40 mg oral cantly increased in high males, with a maximum incidence of adenomas in mid- and high dose nificantly increased the and high dose males and gland (a gland of the higher in high dose mice

observed in a microbial of *Salmonella typhimu-* liver metabolic activation. genetic material was assay using rat or mouse cell forward mutation ation study in CHO cells, ion assay in mouse bone

creased spermatogenesis, giant cell formation were day. Similar findings were No drug-related effects with lovastatin in rats. drug in this class, there treated for 34 weeks at this effect was not observed this same dose was ad- cycle of spermatogenesis, In rats treated with this mg/kg/day, seminiferous loss of spermatogenic epi- vacuolic changes were ob- either study. The clinical nuclear

been established. Lovasta- skeletal malformations at exposure (for mouse fetus) (for rat fetus) based on 800 mg/kg/day). No drug- other species at multiples of 8 on surface area. No evi- in rabbits at exposures up dose of 15 mg/kg/day, high- of congenital anomalies uterine exposure to HMG- has been one report of se- tracheo-esophageal fistula, ation) in a baby born to a dextroamphetamine sul- pregnancy. MEVACOR of child-bearing potential unlikely to conceive and hazards. If the woman MEVACOR, it should be used again as to the poten-

tin is excreted in human another drug in this class is and because of the potential nursing infants, women tak- their infants (see CONTRA-

children and adolescents have children and adolescents are sterol lowering for at least a with this drug is limited (no of 20 years), treatment of recommended at this time.

	MEVACOR (N=613) %	Placebo (N=82) %	Cholestyramine (N=88) %	Probucol (N=97) %
Gastrointestinal				
Constipation	4.9	—	34.1	2.1
Diarrhea	5.5	4.9	8.0	10.3
Dyspepsia	3.9	—	13.6	3.1
Flatus	6.4	2.4	21.6	2.1
Abdominal pain/cramps	5.7	2.4	5.7	5.2
Heartburn	1.6	—	8.0	—
Nausea	4.7	3.7	9.1	6.2
Musculoskeletal				
Muscle cramps	1.1	—	1.1	—
Myalgia	2.4	1.2	—	—
Nervous System/Psychiatric				
Dizziness	2.0	1.2	—	1.0
Headache	9.3	4.9	4.5	8.2
Skin				
Rash/pruritus	5.2	—	4.5	—
Special Senses				
Blurred vision	1.5	—	1.1	3.1
Dysgeusia	0.8	—	1.1	—

	Placebo (N=1663) %	MEVACOR 20 mg q.p.m. (N=1642) %	MEVACOR 40 mg q.p.m. (N=1645) %	MEVACOR 20 mg b.i.d. (N=1646) %	MEVACOR 40 mg b.i.d. (N=1649) %
Body As a Whole					
Asthenia	1.4	1.7	1.4	1.5	1.2
Gastrointestinal					
Abdominal pain	1.6	2.0	2.0	2.2	2.5
Constipation	1.9	2.0	3.2	3.2	3.5
Diarrhea	2.3	2.6	2.4	2.2	2.6
Dyspepsia	1.9	1.3	1.3	1.0	1.6
Flatulence	4.2	3.7	4.3	3.9	4.5
Nausea	2.5	1.9	2.5	2.2	2.2
Musculoskeletal					
Muscle cramps	0.5	0.6	0.8	1.1	1.0
Myalgia	1.7	2.6	1.8	2.2	3.0
Nervous System/Psychiatric					
Dizziness	0.7	0.7	1.2	0.5	0.5
Headache	2.7	2.6	2.8	2.1	3.2
Skin					
Rash	0.7	0.8	1.0	1.2	1.3
Special Senses					
Blurred vision	0.8	1.1	0.9	0.9	1.2

ADVERSE REACTIONS

MEVACOR is generally well tolerated; adverse reactions usually have been mild and transient. Less than 1% of patients were discontinued from controlled clinical studies of up to 14 weeks due to adverse experiences attributable to MEVACOR. About 3% of patients were discontinued from extensions of these studies due to adverse experiences attributable to MEVACOR; about half of these patients were discontinued due to increases in serum transaminases. The median duration of therapy in these extensions was 5.2 years.

In the EXCEL study (see CLINICAL PHARMACOLOGY, *Clinical Studies*), 4.6% of the patients treated up to 48 weeks were discontinued due to clinical or laboratory adverse experiences which were rated by the investigator as possibly, probably or definitely related to therapy with MEVACOR. The value for the placebo group was 2.5%.

Clinical Adverse Experiences

Adverse experiences reported in patients treated with MEVACOR in controlled clinical studies are shown in the table below:

[See first table above.]

Laboratory Tests

Marked persistent increases of serum transaminases have been noted (see WARNINGS).

About 11% of patients had elevations of creatine phosphokinase (CPK) levels of at least twice the normal value on one or more occasions. The corresponding values for the control agents were cholestyramine, 9 percent and probucol, 2 percent. This was attributable to the noncardiac fraction of CPK. Large increases in CPK have sometimes been reported (see WARNINGS, *Skeletal Muscle*).

Expanded Clinical Evaluation of Lovastatin (EXCEL) Study

Clinical Adverse Experiences

MEVACOR was compared to placebo in 8,245 patients with hypercholesterolemia (total cholesterol 240–300 mg/dL [6.2–7.8 mmol/L]) in the randomized, double-blind, parallel, 48-week EXCEL study. Clinical adverse experiences reported as possibly, probably or definitely drug-related in ≥1% in any treatment group are shown in the table below. For no event was the incidence on drug and placebo statistically different.

[See second table above.]

Other clinical adverse experiences reported as possibly, probably or definitely drug-related in 0.5 to 1.0 percent of patients in any drug-related group are listed below. In all these cases the incidence on drug and placebo was not statistically different. *Body as a Whole:* chest pain; *Gastrointestinal:* acid regurgitation, dry mouth, vomiting; *Musculoskeletal:* leg pain, shoulder pain, arthralgia; *Nervous System/Psychiatric:* insomnia, paresthesia; *Skin:* alopecia, pruritus; *Special Senses:* eye irritation.

Concomitant Therapy

In controlled clinical studies in which lovastatin was administered concomitantly with cholestyramine, no adverse reactions peculiar to this concomitant treatment were observed. The adverse reactions that occurred were limited to those reported previously with lovastatin or cholestyramine. Other lipid-lowering agents were not administered concomitantly with lovastatin during controlled clinical studies. Preliminary data suggests that the addition of either probucol or gemfibrozil to therapy with lovastatin is not associated with greater reduction in LDL cholesterol than that achieved with lovastatin alone. In uncontrolled clinical studies, most of the patients who have developed myopathy were receiving concomitant therapy with immunosuppressive drugs, gemfibrozil or niacin (nicotinic acid) (see WARNINGS, *Skeletal Muscle*).

The following effects have been reported with drugs in this class. Not all the effects listed below have necessarily 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-ocular movement, facial paresis), tremor, dizziness, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy, psychic disturbances, 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 erythematous-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal

Continued on next page

Information on the Merck & Co., Inc. products listed on these pages is the full prescribing information from product circulars in use September 30, 1996.

Merck & Co.—Cont.

necrolysis, erythema multiforme, including Stevens-Johnson syndrome.
Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver; and rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma; anorexia, vomiting.
Skin: alopecia, pruritus. A variety of skin changes (e.g., nodules, discoloration, dryness of skin/mucous membranes, changes to hair/nails) have been reported.
Reproductive: gynecomastia, loss of libido, erectile dysfunction.
Eye: progression of cataracts (lens opacities), ophthalmoplegia.
Laboratory Abnormalities: elevated transaminases, alkaline phosphatase, γ-glutamyl transpeptidase, and bilirubin; thyroid function abnormalities.

OVERDOSAGE

After oral administration of MEVACOR to mice the median lethal dose observed was >15 g/m².
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.
Until further experience is obtained, no specific treatment of overdosage with MEVACOR can be recommended.
The dialyzability of lovastatin and its metabolites in man is not known at present.

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 (see NCEP Treatment Guidelines for details on dietary therapy). MEVACOR should be given with meals.
The usual recommended starting dose is 20 mg once a day given with the evening meal. The recommended dosing range is 10–80 mg/day in single or two divided doses; the maximum recommended dose is 80 mg/day. Doses should be individualized according to the recommended goal of therapy (see NCEP Guidelines) and the patient's response (see Tables I to IV under CLINICAL PHARMACOLOGY, *Clinical Studies* for dose response results). Patients requiring reductions in LDL cholesterol of 20% or more to achieve their goal (see INDICATIONS AND USAGE) should be started on 20 mg/day of MEVACOR. A starting dose of 10 mg may be considered for patients requiring smaller reductions. Adjustments should be made at intervals of 4 weeks or more.
In patients taking immunosuppressive drugs concomitantly with lovastatin (see WARNINGS, *Skeletal Muscle*), therapy should begin with 10 mg of MEVACOR and should not exceed 20 mg/day.
Cholesterol levels should be monitored periodically and consideration should be given to reducing the dosage of MEVACOR if cholesterol levels fall significantly below the targeted range.
Concomitant Therapy
Preliminary evidence suggests that the cholesterol-lowering effects of lovastatin and the bile acid sequestrant, cholestyramine, are additive.
Dosage in Patients with Renal Insufficiency
In patients with severe renal insufficiency (creatinine clearance <30 mL/min), dosage increases above 20 mg/day should be carefully considered and, if deemed necessary, implemented cautiously (see CLINICAL PHARMACOLOGY and WARNINGS, *Skeletal Muscle*).

HOW SUPPLIED

No. 3560—Tablets MEVACOR 10 mg are peach, octagonal tablets, coded MSD 730 on one side and MEVACOR on the other. They are supplied as follows:
NDC 0006-0730-61 unit of use bottles of 60.
Shown in Product Identification Guide, page 324
No. 3561—Tablets MEVACOR 20 mg are light blue, octagonal tablets, coded MSD 731 on one side and MEVACOR on the other. They are supplied as follows:
NDC 0006-0731-37 unit of use bottles of 30
NDC 0006-0731-61 unit of use bottles of 60
(6505-01-267-2497, 20 mg 60's)
NDC 0006-0731-94 unit of use bottles of 90
NDC 0006-0731-28 unit dose packages of 100
(6505-01-267-7925, 20 mg 100's)
NDC 0006-0731-78 unit of use bottles of 100
NDC 0006-0731-98 unit of use bottles of 180
NDC 0006-0731-82 bottles of 1000
(6505-01-359-1865, 20 mg 1000's)
NDC 0006-0731-87 bottles of 10,000
(6505-01-379-7905, 20 mg 10,000's).
Shown in Product Identification Guide, page 324
No. 3562—Tablets MEVACOR 40 mg are green, octagonal tablets, coded MSD 732 on one side and MEVACOR on the other. They are supplied as follows:
NDC 0006-0732-61 unit of use bottles of 60
(6505-01-310-0615, 40 mg 60's)
NDC 0006-0732-94 unit of use bottles of 90
NDC 0006-0732-82 bottles of 1000
NDC 0006-0732-87 bottles of 10,000
(6505-01-379-7903, 40 mg 10,000's).
Shown in Product Identification Guide, page 324

Storage
Store between 5–30°C (41–86°F). Tablets MEVACOR must be protected from light and stored in a well-closed, light-resistant container.

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MIDAMOR® Tablets (Amiloride HCl), U.S.P.

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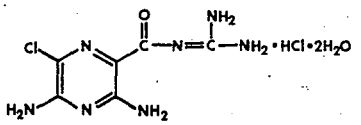
DESCRIPTION

Amiloride HCl, an antikaliuretic-diuretic agent, is a pyrazine-carbonyl-guanidine that is unrelated chemically to other known antikaliuretic or diuretic agents. It is the salt of a moderately strong base (pKa 8.7). It is designated chemically as 3,5-diamino-6-chloro-*N*-(diaminomethylene) pyrazinecarboxamide monohydrochloride, dihydrate and has a molecular weight of 302.14. Its empirical formula is $C_6H_8ClN_7O \cdot HCl \cdot 2H_2O$ and its structural formula is:



MIDAMOR* (Amiloride HCl) is available for oral use as tablets containing 5 mg of anhydrous amiloride HCl. Each tablet contains the following inactive ingredients: calcium phosphate, D&C Yellow 10, iron oxide, lactose, magnesium stearate and starch.

*Registered trademark of MERCK & CO., INC.

CLINICAL PHARMACOLOGY

MIDAMOR is a potassium-conserving (antikaliuretic) drug that possesses weak (compared with thiazide diuretics) natriuretic, diuretic, and antihypertensive activity. These effects have been partially additive to the effects of thiazide diuretics in some clinical studies. When administered with a thiazide or loop diuretic, MIDAMOR has been shown to decrease the enhanced urinary excretion of magnesium which occurs when a thiazide or loop diuretic is used alone. MIDAMOR has potassium-conserving activity in patients receiving kaliuretic-diuretic agents.
MIDAMOR is not an aldosterone antagonist and its effects are seen even in the absence of aldosterone.
MIDAMOR exerts its potassium sparing effect through the inhibition of sodium reabsorption at the distal convoluted tubule, cortical collecting tubule and collecting duct; this decreases the net negative potential of the tubular lumen and reduces both potassium and hydrogen secretion and their subsequent excretion. This mechanism accounts in large part for the potassium sparing action of amiloride.
MIDAMOR usually begins to act within 2 hours after an oral dose. Its effect on electrolyte excretion reaches a peak between 6 and 10 hours and lasts about 24 hours. Peak plasma levels are obtained in 3 to 4 hours and the plasma half-life varies from 6 to 9 hours. Effects on electrolytes increase with single doses of amiloride HCl up to approximately 15 mg.
Amiloride HCl is not metabolized by the liver but is excreted unchanged by the kidneys. About 50 percent of a 20 mg dose of MIDAMOR is excreted in the urine and 40 percent in the stool within 72 hours. MIDAMOR has little effect on glomerular filtration rate or renal blood flow. Because amiloride HCl is not metabolized by the liver, drug accumulation is not anticipated in patients with hepatic dysfunction, but accumulation can occur if the hepatorenal syndrome develops.

INDICATIONS AND USAGE

MIDAMOR is indicated as adjunctive treatment with thiazide diuretics or other kaliuretic-diuretic agents in congestive heart failure or hypertension to:

a. help restore normal serum potassium levels in patients who develop hypokalemia on the kaliuretic diuretic
b. prevent development of hypokalemia in patients who would be exposed to particular risk if hypokalemia were to develop, e.g., digitalized patients or patients with significant cardiac arrhythmias.

The use of potassium-con[illegible] in patients receiving di[illegible] hypertension when [illegible] MIDAMOR has little a[illegible] effect when added to a [illegible] MIDAMOR should rare[illegible] pared with thiazides) di[illegible] Used as single agents, po[illegible] MIDAMOR, result in an [illegible] proximately 10% with [illegible] used alone only when per[illegible] mented and only with ca[illegible] monitoring of serum elec[illegible]

CONTRAINDICATIONS

Hyperkalemia
MIDAMOR should not be [illegible] serum potassium levels [illegible]
Antikaliuretic Therapy [illegible]
MIDAMOR should not be [illegible] potassium-conserving a[illegible] triamterene. Potassium su[illegible] ication, potassium-contai[illegible] sium-rich diet should not be [illegible] severe and/or refractory [illegible] comitant therapy can be [illegible] in serum potassium level[illegible] is used, careful monitoring [illegible] necessary.
Impaired Renal Function [illegible]
Anuria, acute or chronic re[illegible] diabetic nephropathy are [illegible] MIDAMOR. Patients with [illegible] pairment (blood urea nitro[illegible] 100 mL or serum creatinine [illegible] diabetes mellitus should be [illegible] ful, frequent and continuin[illegible] lytes, creatinine, and BUN [illegible] ciated with the use of an ant[illegible] in the presence of renal im[illegible] rapid development of hyp[illegible]
Hypersensitivity [illegible]
MIDAMOR is contraindicated [illegible] sitive to this product.

WARNINGS

Hyperkalemia

Like other potassium-con[illegible] cause hyperkalemia (serum [illegible] than 5.5 mEq per liter) w[illegible] tially fatal. Hyperkalemia [illegible] 10%) when amiloride is [illegible] uretic. This incidence is g[illegible] impairment, diabetes mell[illegible] nized renal insufficiency). [illegible] MIDAMOR is used concom[illegible] uretic in patients without [illegible] of hyperkalemia is reduced [illegible] thus essential to monitor [illegible] fully in any patient receiv[illegible] when it is first introduced [illegible] adjustments, and during [illegible] renal function.

The risk of hyperkalemia may [illegible] conserving agents, including [illegible] concomitantly with an ang[illegible] hibitor. (See PRECAUTIONS [illegible] signs or symptoms of hyper[illegible] muscular weakness, fatigue, [illegible] ties, bradycardia, shock, and [illegible] of the serum potassium level [illegible] kalemia is not usually asso[illegible] When abnormal, the ECG m[illegible] primarily by tall, peaked T [illegible] ous tracings. There may also [illegible] increased depth of the S wave [illegible] ance of the P wave, progres[illegible] plex, prolongation of the PR [illegible]
Treatment of hyperkalemia: [illegible] tients taking MIDAMOR [illegible] immediately. If the serum [illegible] per liter, active measures sho[illegible] measures include the intrav[illegible] bicarbonate solution or or[illegible] rapid-acting insulin prepara[illegible] change resin such as sodium [illegible] given orally or by enema. P[illegible] lemia may require dialysis. [illegible]
Diabetes Mellitus [illegible]
In diabetic patients, hyperk[illegible] the use of all potassium-co[illegible] MIDAMOR, even in patients [illegible]