CME quiz discussion

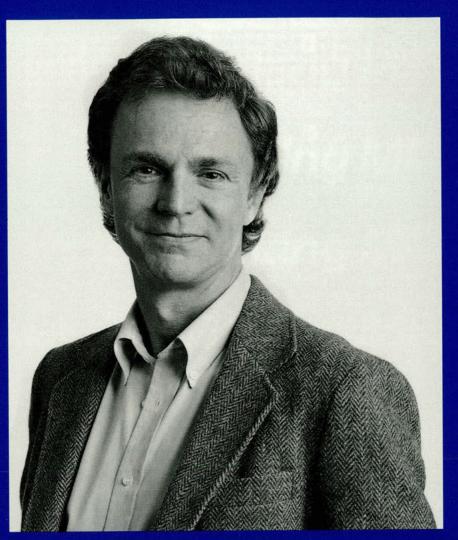
These discussions relate to the September 1988 JAOA CME quiz.

1. (c). There is no consensus about the optimal dose, frequency of administration, or the method of regulating heparin.

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1A. Title of Publication	18. PUBLICATION	
JAOA-JOURNAL OF THE AMERICAN OSTEOPATHIC	ASSOC'N 0 0 9 8 6 1	5 1 09/30/88
3. Frequency of Issue	3A. No. of Issues Publishe Annually	ed 38. Annual Subscription Price
Monthly	12	\$10.00
4. Complete Mailing Address of Known Office of Publication (Street, Cit	ty, County, State and ZIP+4 Code) (Not printer	1)
142 East Ontario Street, Chicago, Cook (County, IL 60611-2864	
5. Complete Mailing Address of the Headquarters of General Business	Offices of the Publisher (Not printer)	
142 East Ontario Street, Chicago, Cook (County, IL 60611-2864	
6. Full Names and Complete Mailing Address of Publisher, Editor, and Publisher (Name and Complete Mailing Address)	Managing Editor (This item MUST NOT be b	lank)
		** 60611 2064
American Osteopathic Association, 142 Eas Editor (Name and Complete Mailing Address)	st Untario Street, Chicag	jo, 11 60611-2864
Thomas W. Allen, DO 142 East Ontario St.	, Chicago, IL 60611-286	
Menaging Editor (Name and Complete Mailing Address)	, Chicago, 15 60611-286	14
Andrea Dzik, 142 East Ontario Street, (Thicago II 60611-2964	
 Owner (If owned by a corporation, its name and address must be stated and I percent or more of total amount of stock. If not owned by a corporation to or other unincorporated firm, its name and address, as well as that of each 	t asso immediately thereunaer the names and ad he names and addresses of the individual owner, individual must be given. If the publication is no	aresses of stockholders owning or notding s must be given. If owned by a partnership oblished by a nonprofit organization, its
or other unincorporated firm, its name and address, as well as that of each is name and address must be stated.) (Item must be completed.)		
Full Name	Complete	Mailing Address
American Osteopathic Association	142 East Ontario Stre	
(a nonprofit organization)	Chicago, IL 60611-2	1864
 Known Bondholders, Mortgagees, and Other Security Holders Ownin Securities (If there are none, so state) 	ng or Holding 1 Percent or More of Total A	mount of Bonds, Mortgages or Other
None Full Name	Complete	Mailing Address
None		
SEPULCIAL CONTRACTOR OF THE SECOND CONTRACTOR		
9. For Completion by Nonprofit Organizations Authorized To Mail at Sp	pecial Rates (DMM Section 423.12 only)	
The purpose, function, and nonprofit status of this organization and	the exempt status for Federal income tax	purposes (Check one)
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- 2. (e). The various fluctuations in half-life does not cause difficulty in deciding on a standard dosage schedule of heparin.
- 3. (c). Secundum-type defects of the atrial septum have been associated with mitral valve prolapse (MVP). MVP has a female dominance.
- 4. (c). In diagnosing MVP, patients with systolic click and mid-tolate systolic murmur must be examined for developmental anomalies. Patients with scoliosis, straight back, thoracic lordosis, or pectus excavatum should undergo echocardiography.
- 5. (b). Although many persons with arteriovenous fistulas remain asymptomatic, ischemic symptoms distal to the fistula are common and referable to the organ involved. Systemic symptoms include high-output cardiovascular failure and pulmonary hypertension.
- 6. (b). The therapeutic approach for traumatic arteriovenous fistula is arterial surgical reconstruction, either via bypass or arteriorrhaphy.
- 7. (e). Acute eosinophilic pneumonia has been associated with the oral administration of penicillin, ampicillin, tetracycline, and nitrofurantoin.
- 8. (b). Flushing the parts of a triple lumen catheter daily does not insure that it is working and in proper position. It is necessary to aspirate the ports daily to determine their position within the central venous system.
- 9. (c). Delayed hydromediastinum after central venous catheterization is the result of phlebitis and necrosis of the vessel wall infusion.

Who's taking MEVACOR®?



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 response to nonpharmacologic measures has been inadequate.

MEVACOR is contraindicated in patients who are hypersensitive to any component of the medication; in patients with active liver disease or unexplained persistent transaminase elevations; in pregnant or lactating patients; and in women of childbearing age, except when such patients are highly unlikely to conceive.

It is recommended that liver function tests be performed before treatment begins, every 4 to 6 weeks during the first 15 months of therapy, and periodically thereafter in all patients.

The effect of lovastatin-induced changes in serum lipoprotein levels, including reduction of serum cholesterol, on cardiovascular morbidity or mortality has not been established.

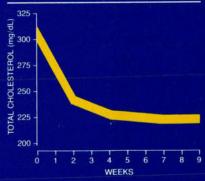
For more details on warnings, precautions, and adverse reactions, including cautionary information regarcing liver dysfunction, myopathy, and slit-lamp monitoring, please see Prescribing Information.

For a Brief Summary of Prescribing Information, please see the following page.

Patient J.D.

- Male, age 42, asymptomatic for cardiac disease
- Father and paternal uncle died of premature coronary heart disease
- Elevated total cholesterol of 305 mg/dL after adequate trial of a cholesterol-lowering diet
- After 7 weeks on MEVACOR, total cholesterol is 223 mg/dL (dosage: 20 mg b.i.d.)

Results with MEVACOR



Not everyone will respond as did the patient in this hypothetical case history; however, the mean reduction in total cholesterol in clinical trials was 17% at 20 mg once a day and 27% at 20 mg b.i.d.





CONTRAINDICATIONS

Hypersensitivity to any component of this medication

Active liver disease or unexplained persistent elevations of serum transaminases.

Pregnancy and lactation

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. Moreover, 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® (Lovastatin, MSD) to decrease the synthesis of cholesterol and possibly other products of the cholesterol. CoA reductase such as MEVACOR* (Lovastatin, MSD) to decrease the synthesis of cholesterol and possibly other products of the cholesterol biosynthesis pathway. MEVACOR may cause fetal harm when admin-istered to a pregnant woman. Therefore, lovastatin is contraindicated during pregnancy. Lovastatin should be administered to women of child-bearing 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 adult patients who received lovastatin for at least one year (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 lovestation and were not received with funders. lovastatin and were not associated with jaundice or other clinical signs or

lovastatin and were not associated with 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 areas of local hepatitis. In this patient, transaminase levels returned to normal following discontinuation of therapy. Some of these patients had abnormal liver function tests prior to lovastatin therapy and/or consumed substantial quantities of alcohol. It is recommended that liver function tests be performed before treatment begins, every 4 to 6 weeks during the first 15 months of therapy with lovastatin, and periodically thereafter in all patients. 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. Liver biopsy should be considered if elevations are persistent beyond the discontinuation of the drug.

The drug should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease.

stantial 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 3 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 were often transient, were not accompar interruption of treatment was not required.

Skeletal Muscle

Myaligh has been associated with lovastatin therapy. Transient, mildly elevated creatine phosphokinase levels are commonly seen in lovastatin-treated patients. However, in clinical trials, approximately 0.5% of patients developed a myopathy, i.e., myaligh are muscle weakness associated with markedly elevated CPK levels. In clinical trials and since the drug was marketed, there have been rare reports of severe rhabdomyolysis that precipitated acute renal failure, especially in cardiac transplant patients on immunosuppressive therapy including cyclosporine. 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 constitute of the control of the 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

diagnosed.

Most of the patients who have developed myopathy while taking lovastatin were receiving concomitant therapy with immunosuppressive drugs, gernfibrozii, or lipid-lowering doses of niacin (nicotinic acid). In clinical trials, about 30% of patients on concomitant immunosuppressive therapy including cyclosporine developed myopathy; the corresponding percentages for gernfibrozil and niacin were approximately 5% and 2%, respectively. It is not known whether the same phenomenon occurs with fibrates other than gernfibrozil. Therefore, the benefits and risks of using lovastatin concomitantly with immunosuppressive drugs, fibrates, or lipid-lowering doses of niacin (nicotinic acid) should be carefully considered. considered.

In 6 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 4 times the expected levels. Because of an apparent relationship between increased plasma levels of active metaboapparent 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 DOS-AGE AND ADMINISTRATION). Even at this dosage, the benefits and risks of using lovastatin in patients taking immunosuppressants should be carefully considered.

Consideration should be given to temporarily withholding or discontinuing drug therapy in any patient with a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis, including; severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine, or electrolyte disorders, and uncontrolled seizures.

PRECAUTIONS

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).

Eye
There was a high prevalence of baseline lenticular opacities in the patient population included in the clinical trials with lovastatin. During these trials the appearance of new opacities was noted. The causal relationship of lovastatin to these findings has not been established.

Of 431 patients examined with sit lamp at baseline and during therapy with lovastatin, 34 had opacities reported at the final examination (5 to 15 months after starting lovastatin) that were not noted at baseline. On the other hand, in 45 patients, opacities observed at baseline were not noted

at the final examination, so that the prevalence did not increase. There was at the linal examination, so that the prevalence did not increase. Inere was no clinically significant change in visual activity 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 activity. Nevertheless, until further experience is obtained, it is recom-mended that patients placed on lovastatin therapy be examined with a slit lamp before or shortly after initiation of treatment and annually thereafter

Homozygous Familial Hypercholesterolemia MEVACOR* (Lovastatin, MSD) is less effective in patients with the rare homozygous familial hypercholesterolemia, possibly because these pa-tients have no functional LDL receptors. MEVACOR appears to be more likely to raise serum transaminases (see ADVERSE REACTIONS) in these homozygous patients

Drug Interactions

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

Coumarin Anticoagulants: In a clinical trial in warfarin-treated patients designed specifically to observe a potential effect of lovastatin on the prooesigned specificacy to observe a potential enter of rovastatin on the pro-thrombin time, lovastatin in dosages up to 40 mg b.i.d. did not produce any consistent alteration of the anticoagulant action of warfarin. However, since the drug was marketed, clinically evident bleeding and/or increased pro-thrombin time have been reported in a few patients taking coumarin anticoagulants concomitantly with lovastatin. The causal relationship to lovastatin is unclear. Nevertheless, it is recommended that in patients invasiant is unicear. Nevertiness, it is recommended that in patients taking anticoagulants, prothorombin time be determined before starting lovastatin and frequently enough during early therapy to insure that no significant alteration of prothorombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the 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.

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Antipyrine: Antipyrine: a model for drugs metabolized by the microsomal hepatic enzyme system (cytochrome P450 system). Because lovastatin had no effect on the pharmacokinetics of antipyrine, interactions with other drugs metabolized via this mechanism are not expected.

Propranolol: In normal volunteers, there was no clinically significant

pharmacokinetic or pharmacodynamic interaction with concomitant ad-ministration of single doses of lovastatin and propranolol. *Digoxin*: In patients with hypercholesterolemia, concomitant admin-

istration of lovastatin and digoxin resulted in no effect on digoxin plasma

Other Concomitant Therapy: Although specific interaction studies were not performed, in clinical studies, lovastatin was used concomitantly with beta blockers, calcium channel blockers, diuretics, and nonsteroidal antiinflammatory drugs (NSAIDs) without evidence of clinically significant adverse interactio

Drug/Laboratory Test Interactions

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

Catanogenesis, watagenesis, impairment of retruity in a 21-month carcinogenic study in mice, a statistically significant (p<0.05) increase in the incidence of hepatocellular carcinomas and adenomas was observed at doses of 500 mg/kg/day (312 times the maximum recommended human dose) of lovastatin. These changes were not seen in mice given doses of 20 and 100 mg/kg/day (12.5 and 62.5 times the maximum recommended human dose).

times the maximum recommended numan dose). A statistically significant increase (psc 10.5b) in the incidence of pulmonary adenomas was seen in female mice receiving 500 mg/kg/day (312 times the maximum recommended human dose); no similar changes were seen in males at any dose or in females receiving 20 or 100 mg/kg/day (12.5 or 62.5 times the maximum recommended human dose). individualy (12.5) to 2.5 mines the maximum recommended human doses. Because the incidence of pulmonary tumors was within the range of untreated animals in studies of similar duration, the relationship of this latter change to treatment is not known. In addition, an increase in the incidence of papilloma in the non-glandular mucosa of the stomach was observed in mice receiving 100 and 500 mg/kg/day (62.5 and 312 times the maximum recommended human

500 mg/kg/day (62.5 and 312 times the maximum recommended human dose); no increase was seen at a dosage of 20 mg/kg/day (12.5 times the maximum recommended human dose). The glandular mucosa was not affected. The human stomach contains only glandular mucosa. Importantly, there is a strong association between this change and hyperplasia of the squamous epithelium (acanthosis) in this region; acanthosis is a characteristic change observed in the non-glandular mucosa of rodents treated with HMG-CoA reductase inhibitors and is most probably a result of inhibition of the reductase in this tissue.

Similar squamous epithelium is found in the esophagus and anorectal unction of the mouse and rat; however, no evidence of a similar drug-induced hyperplastic response was observed in these tissues in studies of up to 21 months in the mouse given up to 500 mg/kg/day (312 times the maximum recommended human dose), or in a study of 24 months in the rat given 180 mg/kg/day (112 times the maximum recommended

numan dose). In a 24-month carcinogenicity study in rats, there was a positive dose response relationship for hepatocellular carcinogenicity in males (unadjusted p=0.025). However, because the incidence of hepatocellular carcinogenicity observed in male rats in this study is similar to that observed spontaneously in this strain of rat, the implications of this finding are

No evidence of mutagenicity was observed in a microbial mutagen test using mutant strains of Salmoneila typhimurium with or without rat or mouse liver metabolic activation. In addition, no evidence of damage to genetic material was noted in an in vitro alkaline elution assay using rat or mouse hepatocytes, a V-79 mammalian cell forward mutation study, an in vitro chromosome aberration study in CHO cells, or an in vivo chromosomal aberration assay in mouse bone marrow.

No drug-related effects on fertility were found in studies with rats.

Pregnancy
Pregnancy Category X
See CONTRAINDICATIONS.

Lovastatin has been shown to produce skeletal malformations in the rat Lovastatin has been snown to produce skeletal malformations in the rat fetus at doses of 800 mg/kg/dg (500 times the maximum recommended human dose). At similar doses in mice, an increase in skeletal malformations was observed. These individual changes are within the range of those observed spontaneously in this strain of mouse. No drug-induced changes were seen in either species at doses of up to 80 mg/kg/day (50 times). times the maximum recommended human dose). No evidence of malfor-mations was noted in rabbits at up to 15 mg/kg/day (highest tolerated dose-about 9 times the maximum recommended human dose). There are no data in pregnant women

Nursing Mothers

Studies in rats have shown that lovastatin is excreted in the milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from MEVACOR, women tak lovastatin should not nurse their infants (see CONTRAINDICATIONS)

Pediatric Use

Safety and effectiveness in children have not been established. Because children are not likely to benefit from cholesterol lowering for at least a decade and because experience with this drug is limited (no studies in subjects below the age of 20 years), treatment of children with lovastatin is not recommended at this time.

not recommended at this time.

ADVERSE REACTIONS

MEVACOR** (Lovastatin, MSD) is generally well tolerated; adverse reactions usually have been mild and transient. Less than 1% of patients were discontinued from controlled clinical studies due to adverse experiences attributable to MEVACOR. About 2% of patients were discontinued from all studies (controlled and uncontrolled) due to adverse experiences attributable to MEVACOR; about one-third of these patients were discontinued due to increases in serum transaminases. tinued due to increases in serum transaminases.

Clinical Adverse Experiences

Adverse experiences reported in patients treated with MEVACOR in

	MEVACOR (N = 613)	Placebo (N = 82)	Cholestyramine (N = 88) %	Probuco (N = 97) %
Gastrointestinal			The Section	1000
Constipation	4.9	1000	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	2.1 5.2
Heartburn	1.6	-	8.0	-
Nausea	4.7	3.7	9.1	6.2
Musculoskeletal				
Muscle cramps	1.1	The same	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	1	4.5	-
Special Senses				
Blurred vision	1.5	-	1.1	3.1
Dysgeusia	0.8	-	1.1	-

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% and probucol, 2%. This was attributable to the noncardiac fraction of CPK. Large increases in CPK have rarely been reported (see WARNINGS, Skeletal Muscle).

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 concommant treatment were observed. The adverse reactions that occurred were limited to those reported previously with lovastatin or cho-lestyramine. Other lipid-lowering agents were not administered concomitantly with lovastatin during controlled clinical studies. In uncontrolled clinical studies, most of the patients who have developed myopathy were receiving concomitant therapy with immunosuppressive drugs, genfibrozil, or niacin (nicotinic acid) (see WARNINGS, Skeletal Muscle).

Uncontrolled Clinical Studies

Uncontrolled Clinical Studies

The adverse experiences observed in uncontrolled studies were similar to those seen in controlled clinical studies. Abnormal liver function tests were observed at a higher incidence than in the controlled studies (see WARNINGS, Liver Dysfunction). Myopathy (myalgia with marked Cycle elevations) was reported in approximately 0.5% of patients (see WARNINGS. INGS. Skeletal Muscle)

Causal Relationship Unclear

Nervous System: A single case of peripheral neuropathy has been reported; the relationship to lovastatin is uncertain. Visual evoked response, nerve conduction measurements, and electromyography in over 30 patients showed no evidence of neurotoxic effects of lovastatin.

So patients showed no evidence or neurotoxic erfects of lovastatin.

Special Senses: 01 431 patients examined with slit lamp at baseline and during therapy with lovastatin, 34 had opacities reported at the final examination (5 to 15 months after starting lovastatin) that were not noted at baseline. On the other hand, in 45 patients, opacities observed at baseline were not noted at the final examination, so that the prevalence did not increase (see PRECAUTION).

not increase (see PPELAUTIONS).

WERDOSAGE

The oral LD₅₀ of MEVACOR in mice is 20 g/kg.

The 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 52 20-mg tablets (1.04 g).
Until further experience is obtained, no specific treatment of over-

dosage with MEVACOR can be recommended.
The dialyzability of lovastatin and its metabolites in man is not known at

DOSAGE AND ADMINISTRATION

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. MEVACOR should be given with meals.

The recommended starting dose is 20 mg once a day given with the evening meal. The recommended dosing range is 20 to 80 mg/day in single or divided doses; the maximum recommended dose is 80 mg/day. Adjustments of dosage should be made at intervals of 4 weeks or more.

Doses should be individualized according to the patients' response (see Doses should be individualized according to the patient's response (see Tables I to IV under CLINICAL PHARMACOLOGY, Clinical Studies for dose response results).

For those patients with severely elevated serum cholesterol levels (i.e., 300 mg/dL [7.8 mmol/L] on diet), MEVACOR may be initiated at 40

In patients taking immunosuppressive drugs concomitantly with lova-statin (see WARNINGS, Skeletal Muscle), the maximum recommended

dosage is 20 mg/day.

Cholesterol levels should be monitored periodically and consideration should be given to reducing the dosage of MEVACOR if cholesterol levels fall below the targeted range.

HOW SUPPLIED

Tablets MEVACOR 20 mg are light blue, octagonal tablets, coded MSD 731 on one side and MEVACOR on the other. They are supplied in unit-of-use bottles of 60 and in unit-dose packages of 100.



For more detailed information, consult your MSD Representative or see Prescribing Information, Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19486



Aspirin and NSAIDs work in arthritis. But they can give you headaches.

Headache #1-GI upset.

The GI upset that aspirin and other NSAIDs can cause is one of the reasons many physicians have switched to Disalcid. NSAIDs and the acetyl radical of aspirin can suppress serum PGE₂ up to 100%. PGE₂ is cytoprotective of the gastric mucosa. Disalcid, which lacks the acetyl radical, causes only minimal suppression of this important prostaglandin. This may be the reason that Disalcid is less likely to cause the GI erosions and blood loss seen with aspirin and other NSAIDs.¹

The efficacy of Disalcid proven in major study.

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the efficacy of Disalcid on the classic parameters by which all antiarthritics are measured.²

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Please see adjacent page for brief summary of prescribing information.