CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-766/S014

Trade Name: Zocor Tablets

Generic Name: Simvastatin

Sponsor: Meck & Co, Inc.

Approval Date: June 9, 1995
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
19-766/S014

APPROVAL LETTER
Merck & Co., Inc.
Attention: Robert Silverman, M.D., Ph.D.
Director, Regulatory Affairs
BLA-30
WEST POINT PA 19486

Dear Dr. Silverman:

Please refer to your May 9, 1995, supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zocor (simvastatin) Tablets.

This supplemental application, "Special Supplement - Changes Being Effected," provides for revisions, including editorial revisions, in the package insert in the following sections:

1. WARNINGS

   Under the Liver Dysfunction and Skeletal Muscle headings - to include editorial revisions.

2. PRECAUTIONS

   a. Under the "Warfarin" heading in the Drug Interactions subsection - to include data from the Oxford Pilot study regarding increase in prothrombin time.

   b. In the Carcinogenesis, Mutagenesis, Impairment of Fertility subsection - to include an editorial revision.

3. HOW SUPPLIED

   To state that tablets are coded with "ZOCOR" on one side.

We have completed our review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the May 9, 1995, final printed labeling. Accordingly, the supplemental application is approved.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.
Should you have any questions, please contact:

Stephen T. Trostle  
Consumer Safety Officer  
Telephone: 301-443-3520.

Sincerely yours,

\[\text{Signature} \quad 6/7/95\]

Solomon Sobel, M.D.  
Director  
Division of Metabolism and  
Endocrine Drug Products, HFD-510  
Center for Drug Evaluation and Research

cc:

Original NDA  
DISTRICT OFFICE (with labeling)  
HF-2/MEDWATCH (with labeling)  
HFD-85 (with labeling)  
HFD-240 (with labeling)  
HFD-638 (with labeling)  
HFD-735/DBarash (with labeling)  
HFD-510  
HFD-510/SAurecchia/WBerlin/EBarbehenn  
HFD-510/STrostle/06/01/95/ft/stt/06/09/95  
N19766AP.014  
ST 06/09/95

Section affected:  
WARNINGS  
PRECAUTIONS  
HOW SUPPLIED

Concurrence:  
EBarbehenn, AJordan 06.02; WBerlin 06.05; YCHiu 06.07;  
SAurecchia, GTroendle, EGalliers 06.08.95

SUPPLEMENT APPROVAL  
(AP: NDA 19-766/S-014)
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
19-766/S014

LABELING
ZOCOR® (Simvastatin)

DESCRIPTION

ZOCOR® (Simvastatin) is a cholesterol lowering agent that is derived synthetically from a fermentation product of Aspergillus terreus. After oral ingestion, simvastatin, which is an inactive lactone, is hydrolyzed to the corresponding β-hydroxy acid form. This is 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.

Simvastatin is butanoic acid, 2,2-dimethyl-1, 2,3,7,8a-heptahydro-3,7-dimethyl-8a,12-dihydroxy-4-hydroxy-6-oxo-2H-pyran-2-yl-ethyl]-1-naphthalenyl esters (1S,10c3a,7B,8B,9S,4S,7-Bap). The empirical formula of simvastatin is C27H39O8S and its molecular weight is 418.57. Its structural formula is:

Simvastatin is a white to off-white, nonhygroscopic, crystalline powder that is practically insoluble in water, and freely soluble in chloroform, methanol and ethanol.

Tablets ZOCOR® for oral administration contain either 5 mg, 10 mg, 20 mg, or 40 mg of simvastatin and the following inactive ingredients: cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, iron oxides, lactose, magnesium stearate, starch, talc, titanium dioxide and other ingredients. Butylated hydroxyanisole is added as a preservative.

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-CPT), coordinated by the National Institutes of Health (NIH), studied men aged 35-59 with total cholesterol levels of 265 mg/dL (6.8 mmol/L) or greater, LDL cholesterol values of 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 revealed that simvastatin significantly reduced total cholesterol, LDL cholesterol, triglycerides, and increased HDL cholesterol.

Follow-up studies have shown that patients receiving simvastatin had a lower incidence of heart disease events, including myocardial infarction, stroke, and death.

CLINICAL STUDIES

ZOCOR® has been shown to be highly effective in reducing total and LDL cholesterol in heterozygous familial and non-familial forms of hypercholesterolemia and in mixed hyperlipidemia. A marked response was seen within 2 weeks, and the maximum therapeutic response occurred within 4-6 weeks. The response was maintained during chronic therapy.

In a multicenter, double-blind, placebo-controlled, response study in patients with familial or non-familial hypercholesterolemia, ZOCOR® given as a single dose in the evening (the recommended dosing) was similarly effective as when given in a twice-daily fashion. ZOCOR® consistently and significantly decreased total plasma cholesterol (TOTAL-C), LDL cholesterol (LDL-C), total cholesterol/HDL cholesterol (TOTAL-C/HDL-C) ratio. ZOCOR® also modestly decreased triglycerides (TRIG) and produced increases of variable magnitude.
density lipoprotein cholesterol are known risk factors for coronary heart disease. The Lipid Research Clinics Coronary Primary Prevention Trial (LRCPPT), coordinated by the National Institutes of Health (NIH), studied men aged 35-59 with total cholesterol levels of 295 mg/dL (7.6 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.

ZOCOR has been shown to reduce both normal and elevated LDL cholesterol concentrations. The effect of simvastatin-induced changes in lipoprotein levels, including reduction of serum cholesterol, on cardiovascular morbidity or mortality has not been established.

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

ZOCOR is a specific inhibitor of HMG-CoA reductase, the enzyme that catalyzes the conversion of HMG-CoA to mevalonate. This early step in the biosynthetic pathway for cholesterol.

**Pharmacokinetics**

Simvastatin is a lactone that is readily hydrolyzed in vivo to the corresponding β-hydroxyacid, a potent inhibitor of HMG-CoA reductase. Inhibition of HMG-CoA reductase is the basis for an assay in pharmacokinetic studies of the β-hydroxyacid metabolites (active inhibitors) and, following

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**TABLE I**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>TOTAL-C</th>
<th>LDL-C</th>
<th>HDL-C</th>
<th>TRIG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>20</td>
<td>3.4</td>
<td>2.0</td>
<td>1.4</td>
<td>175</td>
</tr>
<tr>
<td>ZOCOR</td>
<td>20</td>
<td>3.4</td>
<td>2.0</td>
<td>1.4</td>
<td>175</td>
</tr>
</tbody>
</table>

**TABLE II**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>TOTAL-C</th>
<th>LDL-C</th>
<th>HDL-C</th>
<th>TRIG</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZOCOR</td>
<td>20</td>
<td>3.4</td>
<td>2.0</td>
<td>1.4</td>
<td>175</td>
</tr>
<tr>
<td>Cholestyramine</td>
<td>20</td>
<td>3.4</td>
<td>2.0</td>
<td>1.4</td>
<td>175</td>
</tr>
</tbody>
</table>

When given on a twice-daily basis, ZOCOR consistently and significantly decreased total plasma cholesterol (TOTAL-C), LDL cholesterol (LDL-C), total cholesterol/HDL cholesterol (TOTAL-C/HDL-C) ratio, and LDL cholesterol/HDL cholesterol (LDL-C/HDL-C) ratio. ZOCOR also modestly decreased triglycerides (TRIG) and produced increases of variable magnitude in HDL cholesterol (HDL-C).

The results of a dose response study in patients with primary hypercholesterolemia are presented in Table I.
In a study designed to evaluate the possible effects of simvastatin on reproductive hormones and sperm characteristics in men with familial hypercholesterolemia, there was a small decrease in the mean percentage of motile sperm and a small increase in the mean percentage of abnormal forms, with these changes achieving statistical significance at week 14. However, there was no effect on number or concentration of motile sperm. Simvastatin had no effect on basal reproductive hormone levels (prolactin, luteinizing hormone, follicle-stimulating hormone, and plasma testosterone, provocative testing (PGC stimulation) was not done. Treatment with another HMG-CoA reductase inhibitor resulted in a statistically significant decrease in plasma testosterone.

In a study to evaluate the effect of simvastatin on adrenocortical function in patients with Type II hypercholesterolemia, simvastatin had no effect on basal adrenocortical function as assessed by determination of morning plasma cortisol levels, with free cortisol and urinary excretion of 17-hydroxy steroids. Simvastatin also had no effect on adrenocortical reserve evaluated by the plasma cortisol response to ACTH stimulation and insulin-induced hypoglycemia.

INDICATIONS AND USAGE

Therapy with lipid-lowering agents should be a component of multiple-risk-factor intervention in individuals at significantly increased risk of atherosclerotic vascular disease due to hypercholesterolemia. ZOCOR 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)*, where the response to a diet restriction is inadequate. Secondary causes of hypercholesterolemia (e.g., hypertriglyceridemia, hypothyroidism, nephrotic syndrome, diabetes, obstructive liver disease, other drug therapy, alcoholism, and other hypercholesterolemic conditions) should be excluded before using ZOCOR. Prior to initiating therapy with ZOCOR, secondary causes of hypercholesterolemia (e.g., hypertriglyceridemia, hypothyroidism, nephrotic syndrome, diabetes, obstructive liver disease, other drug therapy, alcoholism, and other hypercholesterolemic conditions) should be excluded before using ZOCOR.

For patients with TG levels greater than or equal to 500 mg/dL, lipid measurements should be performed at intervals of no less than four weeks and should include a repeat fasting lipoprotein profile. This treatment regimen should be continued until the patient's response to therapy has been established and is maintained.
TABLETS

**ZOCOR®**

(SIMVASTATIN)

Circular Number 7825414

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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 many hypertriglyceremic patients, LDL-C may be low or normal despite elevated TOTAL-C. In such cases, ZOCOR is not indicated.

Lipid determinations should be performed at intervals of no less than four weeks and dosage adjusted according to the patient's response to therapy.

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

<table>
<thead>
<tr>
<th>Lipid Category</th>
<th>Risk Factor</th>
<th>Lipid Measurement</th>
<th>Recommended Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C &gt;160 mg/dL</td>
<td>N0, N0</td>
<td>LDL-C &gt;160 mg/dL</td>
<td>OFF, OFF</td>
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<tr>
<td>LDL-C &gt;190 mg/dL</td>
<td>N0, N0</td>
<td>LDL-C &gt;190 mg/dL</td>
<td>OFF, OFF</td>
</tr>
<tr>
<td>LDL-C &gt;220 mg/dL</td>
<td>N0, N0</td>
<td>LDL-C &gt;220 mg/dL</td>
<td>OFF, OFF</td>
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<tr>
<td>LDL-C &gt;240 mg/dL</td>
<td>N0, N0</td>
<td>LDL-C &gt;240 mg/dL</td>
<td>OFF, OFF</td>
</tr>
<tr>
<td>LDL-C &gt;260 mg/dL</td>
<td>N0, N0</td>
<td>LDL-C &gt;260 mg/dL</td>
<td>OFF, OFF</td>
</tr>
<tr>
<td>LDL-C &gt;280 mg/dL</td>
<td>N0, N0</td>
<td>LDL-C &gt;280 mg/dL</td>
<td>OFF, OFF</td>
</tr>
<tr>
<td>LDL-C &gt;300 mg/dL</td>
<td>N0, N0</td>
<td>LDL-C &gt;300 mg/dL</td>
<td>OFF, OFF</td>
</tr>
<tr>
<td>LDL-C &gt;320 mg/dL</td>
<td>N0, N0</td>
<td>LDL-C &gt;320 mg/dL</td>
<td>OFF, OFF</td>
</tr>
<tr>
<td>LDL-C &gt;340 mg/dL</td>
<td>N0, N0</td>
<td>LDL-C &gt;340 mg/dL</td>
<td>OFF, OFF</td>
</tr>
<tr>
<td>LDL-C &gt;360 mg/dL</td>
<td>N0, N0</td>
<td>LDL-C &gt;360 mg/dL</td>
<td>OFF, OFF</td>
</tr>
<tr>
<td>LDL-C &gt;380 mg/dL</td>
<td>N0, N0</td>
<td>LDL-C &gt;380 mg/dL</td>
<td>OFF, OFF</td>
</tr>
<tr>
<td>LDL-C &gt;400 mg/dL</td>
<td>N0, N0</td>
<td>LDL-C &gt;400 mg/dL</td>
<td>OFF, OFF</td>
</tr>
</tbody>
</table>

Coronary heart disease or peripheral vascular disease including symptomatic carotid artery disease.

Other risk factors for coronary heart disease (CHD) include: age (male >55 years, female >65 years), history of premature CHD, diabetes mellitus, metabolic syndrome, renal disease, smoking, obesity, and family history of premature CHD.
ZOCOR® (Simvastatin)

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

CONTRAINDICATIONS

Simvastatin should not be used in patients who have active liver disease, unexplained persistent elevations of serum transaminases, or a history of myopathies, including rhabdomyolysis.

Pregnancy and lactation.

Simvastatin is a pregnancy category X drug. Studies in animals have shown evidence of fetal toxicity (see WARNINGS). It is not known whether simvastatin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when simvastatin is administered to a nursing woman.

WARNINGS

Liver Transaminases

Persistent increases (more than 3 times the upper limit of normal) of serum transaminases have occurred in 5% of patients who received simvastatin. In clinical trials, when drug treatment was interrupted or discontinued, these patients had a return to pretreatment levels. The increases were not associated with jaundice or other clinical signs or symptoms. There was no evidence of histologic liver disease. Persistent increases in transaminases may be accompanied by clinical symptoms and signs of liver disease (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 in dose, and periodically thereafter (e.g., semiannually). Patients who develop increased transaminase levels should be monitored, with a second liver function test performed in the evening. If the finding is confirmed, the drug should be stopped. The patient should be advised to discontinue all other medications which may be associated with increases in transaminases. The drug should not be restarted.

Muscle Pain

Myopathy may rarely occur in patients receiving simvastatin. Myopathy can be associated with or without an elevation in creatine kinase (CK) levels (see ADVERSE REACTIONS). Patients should be advised to discontinue the drug if muscle pain or tenderness or weakness occurs, particularly if accompanied by malaise or fever. If myopathy is diagnosed, it should be treated with discontinuation of the drug. Myopathy may occur in patients receiving less than 20 mg simvastatin daily.

Concomitant Use of Other Drugs

When simvastatin is used in combination with other lipid-lowering agents (e.g., niacin, cholestyramine, or colestipol), the frequency of muscle problems may be increased. Pharmacokinetic interactions with other concomitantly administered drugs may occur (see DRUG INTERACTIONS). In clinical studies, one in 10 volunteers

Skeletal Muscle

Rare cases of rhabdomyolysis with acute renal failure occur.

ZOCOR® (Simvastatin)

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

Myopathy should be considered in any patient with diffuse myalgia, muscle tenderness or weakness, and an elevated level of creatine kinase (CK) (see ADVERSE REACTIONS). If myopathy occurs, simvastatin therapy should be discontinued and repeat CK evaluations should be performed. If markedly elevated CK levels occur or myopathy is diagnosed or suspected, simvastatin should be discontinued.

Other Drugs

Before instituting therapy with ZOCOR, an attempt should be made to control hypercholesterolemia with an appropriate diet, exercise, and weight reduction programs; and to treat other underlying medical problems (see INDICATIONS AND USAGE) and ADVERSE REACTIONS.) This should be considered in the differential diagnosis of chest pain in patients on therapy with simvastatin.

Concomitant use of other drugs (e.g., niacin) may increase the risk of myopathy (see DRUG INTERACTIONS). In clinical studies, one in 10 volunteers
transaminases have been reported following therapy with simvastatin. These changes appeared soon after initiation of therapy with simvastatin, were often transient, were not accompanied by any symptoms and did not require interruption of treatment.

**Muscle**

Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have also been associated with simvastatin. Rhabdomyolysis has also been associated with other HMG-CoA reductase inhibitors when they were administered alone or concomitantly with 1) immunosuppressive therapy, including cyclosporine in cardiac transplant patients, 2) gemfibrozil or lipid-lowering doses (≥ 1 g/day) of niacin in non-transplant patients, or 3) erythropoietin infusions in patients with renal failure. Some of the patients who had rhabdomyolysis in association with the reductase inhibitors had pre-existing renal insufficiency, usually as a consequence of long-standing diabetes. In most subjects, the myopathy was of the unsatisfactory lipid response to other simvastatin or gemfibrozil therapy. The possible benefits of combined therapy with these drugs are not considered to outweigh the risk of severe myopathy, rhabdomyolysis, and acute renal failure. Rhabdomyolysis is associated with the use of other drugs, including ciclosporin. Therefore, the combined use of simvastatin with other fibrate should generally be avoided.

Muscle weakness accompanied by marked elevation of creatine phosphokinase was observed in a renal transplant patient on ciclosporin and simvastatin following the initiation of therapy with the systemic angiotensin II receptor antagonist losartan. Rhabdomyolysis with renal failure has also been reported in a renal transplant patient receiving ciclosporine and another HMG-CoA reductase inhibitor shortly after a dose increase in the latter drug. Losartan is a competitive inhibitor of angiotensin II receptor and has been shown to reduce antihypertensive agents that inhibit cholinergic and adrenergic actions at different points in the biosynthetic pathway. 

Physicians contemplating combined therapy with simvastatin and ciclosporin should consider the potential for drug interactions and should carefully monitor potential for myopathy and renal insufficiency. In one study, ciclosporin concentrations in plasma have been increased by more than 50% in patients on ciclosporin and simvastatin treatment. Patients taking ciclosporin should be monitored closely for changes in renal function and myopathy.

**Liver**

Liver function tests should be monitored during therapy with simvastatin. Transaminase levels, bilirubin levels, and alkaline phosphatase levels should be followed closely, particularly in patients with renal impairment, because of the potential for drug interactions and potential for myopathy and renal insufficiency. In one study, ciclosporin concentrations in plasma have been increased by more than 50% in patients on ciclosporin and simvastatin treatment. Patients taking ciclosporin should be monitored closely for changes in renal function and myopathy.

**Erythropoietin**

In patients receiving erythropoietin, simvastatin should be administered with caution, as it may reduce the effectiveness of the drug.

**Concomitant Therapy**

Although specific interaction studies were not performed, in clinical studies, simvastatin was used concomitantly, with immunosuppressive agents, angiotensin-converting enzyme (ACE) inhibitors, beta blockers, calcium channel blockers, diuretics and nonsteroidal anti-inflammatory drugs (NSAIDs) without evidence of clinical adverse events or interactions. The effect of cholesterol on the efficacy and safety of antihypertensive or antithrombotic medications has not been evaluated.

**Clinical Trials:**

Another study has shown that therapy with gemfibrozil is more effective than placebo in reducing the plasma total cholesterol and LDL cholesterol levels. This effect was observed in patients receiving gemfibrozil and simvastatin, but not in patients receiving simvastatin alone.

**Results of Clinical Trials:**

The effect of gemfibrozil on the rate of adverse events has been evaluated in a multicenter, randomized, double-blind, placebo-controlled trial. The overall incidence of adverse events was similar between the two groups. However, patients receiving gemfibrozil had a higher rate of adverse events related to muscle, such as myalgia and myopathy.

**Conclusion:**

In conclusion, simvastatin is generally well tolerated and safe when used in combination with other medications. However, close monitoring for potential drug interactions and adverse events is recommended.

**References:**

ZOCOR® (Simvastatin)

resulted in a 6 times (rat) or 4 times (rabbit) the human exposure based on mg/m² surface area. However, in studies with another structurally-related HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and rabbits. Human reports of congenital anomalies have been received following intravenous exposure to HMG-CoA reductase inhibitors. There has been one report of severe congenital bone deformity, tracheo-esophageal fistula, and shunt atresia (VATER association) in a baby born to a woman who took another HMG-CoA reductase inhibitor with dextromethorphan sulfate during the first trimester of pregnancy. Simvastatin should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking simvastatin, it should be discontinued and the patient advised again as to the potential hazards to the fetus.

Pediatric Use

Safety and effectiveness in children and adolescents have not been established. Because children and adolescents are not likely to benefit from cholesterol lowering for at least a decade and because experience with this drug was limited in studies where subjects below the age of 20 years, treatment of children or adolescents with simvastatin is not recommended at this time. In the absence of long-term pediatric data, simvastatin should not be used in children (see CONTRAINDICATIONS).

ADVERSE REACTIONS

The controlled clinical studies and the open extensions (2423 patients with mean duration of follow-up of approximately 16 months) 1.4% of patients were discontinued due to adverse experiences, attributable to ZOCOR. Adverse experiences have usually been mild and transient. ZOCOR has been evaluated for adverse reactions in more than 21,000 patients and is generally well tolerated. A few patients have discontinued treatment due to clinical adverse experiences.

Clinical Adverse Experiences

Adverse experiences have occurred in patients taking a 10-mg or greater dose of ZOCOR. Regardless of dosage, in controlled clinical studies, the following adverse experiences have been reported:
The following effects have been reported with doses in this class. Not all the effects listed below have necessarily been associated with simvastatin therapy.

**Skeletal muscle cramps, myalgia, myopathy, rhabdomyolysis, arthralgia.**

**Neurological Dysfunction of certain cranial nerves (including alteration of taste; impairment of extraocular movement, facial paresis), tremor, dizziness, vertigo, monoparesis, paresis, peripheral neuropathy, peripheral nerve palsy, anxiety, insomnia, depression.**

**Hypersensitivity: Reactions:** An apparent hyperviscosity syndrome has been reported rarely which includes one or more features of the following features: anaphylaxis, angioedema, lupus erythematosus-like syndrome; polyarthralgia, polyarthrosis, vasculitis, purpura, synovitis, scleroderma, hemolytic anemia, positive ANA, ESR increased, polyneuropathy, arthritis, arthralgia, urticaria, asthma, photosensitivity, fever, chills, flushing, malaise, dyspnea, edema, guillain, neck stiffness, papilledema, photophobia, myalgia, including Stevens-Johnson syndrome. In some rare cases, signs of fibrosis, atrophy, or atrophy of the soft tissues of the face.

**Gastrointestinal:** pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice. Fatty change in liver, and rarely, cirrhosis, fulminant hepatic necrosis, and hepatocellular carcinoma, vomiting, nausea, growth in weight, liver function tests abnormalities, anorexia, stomach ache, nausea.

**Skin:** alopecia, pruritus. A variety of skin changes, including hair loss, photophobia, dryness of skin, mucous membranes, diarrhea, dyspepsia, rash, peeling, desquamation, acne, dryness of skin, mucous membranes, rash, peeling, desquamation.

**Eye:** progression of cataracts (see section Cautions), photophobia, dryness of skin, mucous membranes, rash, peeling, desquamation.

**Reproductive:** gynecomasia; loss of testicular hair.

**Laboratory Tests**

Marked persistent increases of serum transaminases have been noted (see **WARNINGS**). Liver function test abnormalities, including aminotransferase, alkaline phosphatase, bilirubin, transaminase, and alkaline phosphatase.

**Prednisone: Pregnancy Category X**

Prednisone is not teratogenic in rats at doses of 25 mg/kg/day or in rabbits at doses up to 10 mg/kg daily.
ZOCCOR® (Simvastatin)

... discontinued if the normal value on one or more occasions. This was attributable to the concomitant fraction of CPK. Muscle pain or dysfunction usually was not reported (see WARNINGS, Skeletal/Muscle.

Concomitant Therapy

In controlled clinical studies in which simvastatin 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 simvastatin or cholestyramine. The combined use of simvastatin with fibrates should generally be avoided (see WARNINGS, Skeletal/Muscle.

OVERDOSE

Significant lethality was observed in mice after a single oral dose of 8 g/m². No evidence of lethality was observed in rats or dogs treated with doses of 20 and 100 g/m² respectively. No specific diagnostic signs were observed in rodents. At these doses the only signs seen in dogs were illness and mucoid stools.

No cases of overdose with ZOCCOR have been reported. No patients had any specific symptoms, and all patients recovered without sequelae. The maximum dose was 450 mg. Until further experience is gained, no specific treatment of overdose with ZOCCOR can be recommended.

The oral bioavailability and its metabolites in man is not known at present.

DOSE AND ADMINISTRATION

The patient should be placed on a standard cholesterol-lowering diet before starting ZOCCOR and should continue on this diet during treatment with ZOCCOR (see NCEP Treatment Guidelines for details on dietary therapy).

The recommended starting dose is 5-10 mg ZOCCOR daily in the evening. The recommended dosing range is 5-40 mg/day in the evening. The maximum recommended dose is 40 mg/day. Dosages should be titrated upward as necessary to maintain LDL cholesterol below the recommended levels (see NCEP Guidelines) and the patient's requirements. Patients requiring additional reductions in LDL cholesterol may require 80 mg/day of ZOCCOR. A starting dose of 5 mg should be considered for patients requiring smaller reductions and for the elderly. Adjustments of dosage should be made at intervals of 4 weeks or more.

In the elderly, minimum reductions in LDL cholesterol may be achieved with daily doses of 20 mg of ZOCCOR.

In patients taking immunosuppressive drugs concomitantly with simvastatin (see WARNINGS, Skeletal/Muscle) and should not exceed 10 mg/day to avoid potential liver toxicity. If other cholesterol-lowering drugs are added, the dosage of ZOCCOR should be increased accordingly.
Concomitant Therapy
- ZOOCOR is effective alone or when used concomitantly with other 
  acid suppressants. Use of ZOOCOR with fibrate-type drugs such 
  as gemfibrozil or colchicine should generally be avoided. (see 
  WARNINGS: Skeletal Muscle).

Dosage in Patients with Renal Insufficiency
- Because ZOOCOR does not undergo significant renal extrac-
  tion, modification of dosage should not be necessary in 
  patients with mild to moderate renal insufficiency. However, 
  caution should be exercised when ZOOCOR is administered to 
  patients with severe renal insufficiency; such patients should 
  be started at 5 mg/day and be closely monitored (see CLINI-
  CAL PHARMACOLOGY: Pharmacokinetics and WARNINGS, 
  Skeletal Muscle).

HOW SUPPLIED
- No. 3588 — Tablets ZOOCOR 5 mg are buff, shield-shaped, 
  film-coated tablets, coded MSD 726 on one side and ZOOCOR on 
  the other. They are supplied as follows: 
  NDC 0006-0726-61 unit of use bottles of 60 (0506-01-354- 
  4549, 5 mg 60's)
  NDC 0006-0726-64 unit of use bottles of 90 (0506-01-354- 
  4549, 5 mg 90's)
  NDC 0006-0726-28 unit dose packages of 100.

- No. 3588 — Tablets ZOOCOR 10 mg are peach, shield-
  shaped, film-coated tablets, coded MSD 725 on one side and 
  ZOOCOR on the other. They are supplied as follows: 
  NDC 0006-0725-64 unit of use bottles of 60 (0506-01-354- 
  4549, 10 mg 60's)
  NDC 0006-0725-54 unit of use bottles of 90 (0506-01-354- 
  4549, 10 mg 90's)
  NDC 0006-0729-28 unit dose packages of 100 (0506-01-354- 
  4549, 10 mg individually sealed 100's)

- No. 3590 — Tablets ZOOCOR 25 mg are tan, shield-
  shaped, film-coated tablets, coded MSD 740 on one side and ZOOCOR on 
  the other. They are supplied as follows: 
  NDC 0006-0740-61 unit of use bottles of 60 (0506-01-354- 
  4548, 20 mg 60's)
  NDC 0006-0740-82 bottles of 1000
  NDC 0006-0740-87 bottles of 10000

- No. 3590 — Tablets ZOOCOR 40 mg are brick-red, shield-
  shaped, film-coated tablets, coded MSD 749 on one side and 
  ZOOCOR on the other. They are supplied as follows: 
  NDC 0006-0749-61 unit of use bottles of 60 (0506-01-354-
  4546, 40 mg 60's)

Storage
- Store between 5-30°C (41-86°F).
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
19-766/S014

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS
*Merck Research Laboratories
P.O. Box 4, BLA-30
West Point, PA 19486-0004

Attention: Robert E. Silverman, M.D., Ph.D

Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: ZOCOR
NDA Number: 19-766
Supplement Number: S-014
Date of Supplement: May 9, 1995
Date of Receipt: May 11, 1995

Unless we find the application not acceptable for filing, the filing date will be 60 days from the receipt date above.

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Attention: Document Control Room 14B-03
5600 Fishers Lane, HFD-510
Rockville, MD 20857

Sincerely yours,

[Signature]
Supervisory Consumer Safety Officer
Division of Metabolism and Endocrine Drug Products
Center for Drug Evaluation and Research
May 9, 1995

Solomon Sobel, M.D. - Director
Division of Metabolism and Endocrine Drug Products
HFD-510, Room 14B-04
Office of Drug Evaluation II (CDER)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Sobel:

SPECIAL SUPPLEMENT - CHANGES BEING EFFECTED

NDA 19-766: ZOCOR™ (Simvastatin)

Pursuant to Section 505(b) of the Food Drug and Cosmetic Act and in accordance with 21 CFR 314.70(c), we submit, for your approval, a supplement to NDA 19-766.

As indicated on the attached Form FDA 356h, the supplemental application provides for changes in Item 4.c.ii of the approved New Drug Application for ZOCOR.

The circular (#7825414) has been modified under PRECAUTIONS to strengthen and clarify the existing product label description of potential drug interactions between simvastatin and warfarin based upon results from the pilot phase of the Oxford Cholesterol Study. This supplemental application is organized as a series of attachments:

Attachment 1: Summary of Revisions and Annotated Package Circular
Attachment 2: Rationale for Label Change
Attachment 3: References
Attachment 4: Final Printed Labeling (15 copies)

With this letter, we submit 15 copies of the Final Printed package circular (#7825414), a Summary of Revisions and a draft annotated package circular.

The changes will become effective on June 1, 1995 and will apply to all packages of ZOCOR distributed from the company's manufacturing facilities at West Point, Pennsylvania. It should be noted that this FPL will supersede #7825412 (submitted May 8, 1995). The label revision #7825413 has been discarded due to technical errors discovered prior to release.
We consider the filing of this Supplemental New Drug Application to be a confidential matter, and request the Food and Drug Administration not to make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this supplemental application should be directed to Robert E. Silverman, M.D., Ph.D. (610/397-2944) or, in my absence, Bonnie J. Goldmann, M.D. (610/397-2383).

Sincerely yours,

[Signature]

Robert E. Silverman, M.D., Ph.D.
Director, Regulatory Affairs

Attachments
Circular No. 7825414
Certified #Z 747 795 432

Desk Copy: Mr. S. Trostle, HFD-511, Room 14B-04, Certified #Z 747 795 432
USER FEE DATA ENTRY/VALIDATION FORM

NDA #19766 DOCUMENT ID/LETTER DATE SLR-616/MAY 9, 1995
APPLICANT NAME MERCK
PRODUCT NAME ZOCOR (SIMVASTATIN)

FORM MUST BE COMPLETED ASAP

1. YES User Fee Cover Sheet Validated?

NOTE TO DOCUMENT ROOM:
PLEASE MAKE THE FOLLOWING CHANGES TO THE COMLS DATA ELEMENTS

2. YES NO CLINICAL DATA?
[Check YES if contains study reports or literature reports of what are
explicitly or implicitly represented by the applicant to be adequate and well
controlled-trials. "Clinical data do not include data-used-to-modify-the
labelling to add a restriction that would improve the safe use of the drug
(e.g., to add an adverse reaction, contraindication or warning to the
labeling)."

REF IF NO CLINICAL DATA IN SUBMISSION, INDICATE IF CLINICAL
DATA ARE CROSS REFERENCED IN ANOTHER SUBMISSION?

3. YES NO NDA BEING SPLIT FOR ADMINISTRATIVE CONVENIENCE (OTHER THAN
BUNDLING)? IF YES, list ALL NDA numbers, review divisions & indicate those fo
which application fees apply.
NDA # DIVISION
N_ FEE NO FEE
N_ FEE NO FEE

4. YES NO BUNDLING POLICY APPLIED CORRECTLY? NO DATA ENTRY REQUIRED
FOR ELEMENT
[Check YES if application is properly designated as one application or is
properly submitted as a supplement instead of an original application. Check
NO if application should be split into more than one application or submitted
as an original instead of a supplement. IF NO, list resulting NDA numbers, an
review divisions.]
NDA # DIVISION NDA # DIVISION
N_ _

5. P S PRIORITY OR STANDARD?

6. CEO SIGNATURE/DATE

COPY DISTRIBUTION: ORIGINAL TO ARCHIVAL AFTER DATA ENTRY, ONE COPY EACH TO DIvision FILE AND CON, ASSOCIATE DIRECTOR FOR POLICY NPD-5
**USER FEE COVER SHEET**

**1. APPLICANT'S NAME AND ADDRESS**
Merck Research Laboratories  
P.O. Box 4, BLA-30  
West Point, PA 19486-0004

**2. USER FEE BILLING NAME, ADDRESS, AND CONTACT**
Merck Research Laboratories  
P.O. Box 4, BLA-30  
West Point, PA 19486-0004  
ATTN: Bonnie J. Goldmann, M.D.  
Executive Director  
Regulatory Affairs

**3. TELEPHONE NUMBER (include Area Code)**  (610) 397-2383

**4. PRODUCT NAME**  ZOCOR

**5. DOES THIS APPLICATION CONTAIN CLINICAL DATA?**  NO

**6. USER FEE I.D. NUMBER**

**7. LICENSE NUMBER/ANDA NUMBER**

**8. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.**
- [ ] A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED BEFORE 9/1/92
- [ ] AN INSULIN PRODUCT SUBMITTED UNDER 506
- [ ] THE APPLICATION IS SUBMITTED UNDER 505(b)(2) (See reverse before checking box.)

**FOR BIOLOGICAL PRODUCTS ONLY**
- [ ] WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION
- [ ] BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92
- [ ] A CRUDE ALLERGENIC EXTRACT PRODUCT
- [ ] AN "IN VITRO" DIAGNOSTIC BIOLOGIC PRODUCT LICENSED UNDER 351 OF THE PHS ACT

**9. a. HAS THIS APPLICATION QUALIFIED FOR A SMALL BUSINESS EXCEPTION?**  NO  
(See reverse if answered YES)

**b. HAS A WAIVER OF APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?**  NO  
(See reverse if answered YES)

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This completed form must be signed and accompanied each new drug or biologic product, original or supplement.

**SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE**
Bonnie J. Goldmann, M.D.

**TITLE**  Executive Director  
**REGULATORY AFFAIRS**

**DATE**  May 9, 1995

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FORM FDA 3397 (12/93)