CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-766/S035

Trade Name: Zocor Tablets

Generic Name: simvastatin

Sponsor: Merck & Co., Inc.

Approval Date: September 15, 1999
**APPLICATION NUMBER:**
19-766/S035

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
19-766/S035

APPROVAL LETTER
NDA 19-766/S-035

Merck & Co., Inc.
Attention: Robert E. Silverman, M.D., Ph.D.
Sumneytown Pike, BLA-10
P. O. Box 4
West Point, PA 19486

SEP 15 1999

Dear Dr. Silverman:

Please refer to your supplemental new drug application dated February 16, 1999, received
February 17, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act
for Zocor (simvastatin) Tablets.

We note that this supplement was submitted as a 'Special Supplement - Changes Being Effect ed'
under 21 CFR 314.70(c).

This submission contained final printed labeling and was scheduled to be implemented on or
about July 1, 1999. This supplemental new drug application provides for changes in the labeling
sections of the Zocor package insert. These changes include:

1. Addition of the phrase “HIV protease inhibitors” to the drugs list in WARNINGS,
   Skeletal Muscles, Myopathy caused by drug interaction, and in PRECAUTIONS, Drug
   Interactions.

2. The four tables were editorially reformatted to one style. These revisions are found in
   CLINICAL PHARMACOLOGY, Clinical Studies; INDICATIONS AND USAGE,
   General Recommendations; and ADVERSE REACTIONS.

We have completed the 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 submitted final printed labeling (package insert
submitted February 16, 1999).

We note that the changes in the WARNINGS and PRECAUTIONS sections described above
were incorporated in your supplemental application, S-032 (submitted on October 16, 1998) and
were approved August 5, 1999. Because this supplement has been superseded by supplement-
032, the FPL will not be reviewed, but will be retained in our files.
If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Margaret Simoneau, R.Ph., Regulatory Management Officer, at (301) 827-6418.

Sincerely,

\[\begin{align*}
\text{Solomon Sobel, M.D.} \\
\text{Director} \\
\text{Division of Metabolic and Endocrine Drug Products} \\
\text{Office of Drug Evaluation II} \\
\text{Center for Drug Evaluation and Research}
\end{align*}\]
cc:
Archival NDA 19-766
HFD-510/Div. Files
HFD-510/M. Simoneau
HFD-510/Reviewers and Team Leaders
HF-2/MedWatch (with labeling)
HFD-002/ORM (with labeling)
HFD-102/ADRA (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-21/ACS (with labeling) - for drug discussed at advisory committee meeting.
HFD-095/DDMS-IMT (with labeling)
HFD-820/DNDC Division Director
DISTRICT OFFICE

Drafted by: Mas/August 24, 1999
Initialed by: SShen8.24.99/MParks for Dorloff8.24/99/SMoore and for
final:Mas9.13.99
filename: 17966.35B

APPROVAL (AP)
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
19-766/S035

LABELING
TABLETS
ZOCOR® (SIMVASTATIN)

DESCRIPTION
ZOCOR® (simvastatin) is a lipid-lowering agent that is derived synthetically from a fermentation product of the Streptomyces genus. After oral ingestion, simvastatin, which is an inactive lactone, is hydrolyzed to the corresponding hydroxy-3-(4-methyl-3-nitrophenyl)coumarin A (HMG-CoA reductase). This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is an early rate-limiting step in the biosynthesis of cholesterol.

Simvastatin is 2,2-dimethyl-2,3-dihydro-1H-indene-1-carboxylic acid (256.31 g/mol). The empirical formula of simvastatin is C_{23}H_{27}O_5, and its molecular weight is 415.57 g/mol. Its structural formula is:

Simvastatin is a white, odorless, amorphous, crystalline powder that is practically insoluble in water. It is freely soluble in alcohol, chloroform, methanol, and ethanol.

Each ZOCOR® tablet contains 5 mg, 10 mg, 20 mg, or 40 mg of simvastatin. The tablets contain hydroxypropyl cellulose, lactose, magnesium stearate, starch, and other excipients, which are added as a preservative.

CLINICAL PHARMACOLOGY
The mechanism of action of simvastatin involves the inhibition of HMG-CoA reductase, the rate-limiting step in the biosynthesis of cholesterol.

Following a single oral dose of "C-labeled simvastatin in man, 13% of the dose was excreted in urine and 65% in feces. The latter represents absorbed drug equivalents excreted in bile, as well as any unabsorbed drug. Plasma concentrations of total cholesterol were reduced by 50% within 4 hours and declined rapidly to about 10% of peak by 12 hours.

Absorption of simvastatin was estimated to be the same in different individuals. The peak plasma concentration of simvastatin was observed at about 1 hour after oral administration. The mean absorption of simvastatin was similar in individuals given the medication with food or on an empty stomach.

In a single-dose study in healthy volunteers, the area under the plasma concentration-time curve (AUC) was increased by 14% after the administration of simvastatin with food compared to administration on an empty stomach.

The efficacy of simvastatin was demonstrated in a placebo-controlled, double-blind, parallel-group study in patients with hypercholesterolemia. ZOCOR® was effective as a single dose in reducing total cholesterol and LDL cholesterol levels, as well as in lowering the risk of cardiovascular events and mortality.
response study in patients with familial hypercholesterolemia. ZOCOR was administered in the morning (the recommended dosing) was similar in effect as when given on a twice-daily basis. ZOCOR consistently and significantly decreased total-C, LDL-C, LDL-C/HDL-C, and LDL-C/HDL-C ratio. ZOCOR also decreased LDL-C in 10% of patients.

The results of 3 separate studies, providing the same response to simvastatin in patients with normal hypercholesterolemia are presented in Table 1:

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Dose Response in Patients with Primary Hypercholesterolemia (Mean Percent Change from Baseline After 4-6 Weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TREATMENT</td>
<td>N</td>
</tr>
<tr>
<td>Lower Dose Comparative Study</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>20</td>
</tr>
<tr>
<td>ZOCOR</td>
<td>20</td>
</tr>
<tr>
<td>Placebo</td>
<td>20</td>
</tr>
<tr>
<td>ZOCOR</td>
<td>20</td>
</tr>
<tr>
<td>Higher Dose Comparative Study</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>20</td>
</tr>
<tr>
<td>ZOCOR</td>
<td>20</td>
</tr>
</tbody>
</table>

The mean reduction in LDL-C was 42% at the 10 mg dose, by the 664 patients randomized to receive patients with plasma TG > 500 mg/dL had a median reduction in TG of 40 mg/dL.

In a 12-week, double-blind, placebo-controlled study in 40 patients with primary hypercholesterolemia, ZOCOR reduced LDL-C by 50% at the recommended dose.

ZOCOR is a specific inhibitor of HMG-CoA reductase, the enzyme that catalyzes the conversion of HMG-CoA to mevalonate.  The reduction of LDL-C to medrol is an early step in the biosynthetic pathway for cholesterol.

ZOCOR is a competitive inhibitor of HMG-CoA reductase, with an IC50 of 0.1 nM. Inhibition of HMG-CoA reductase by ZOCOR reduces the formation of cholesterol and its precursors, 16-carbon fatty acids, and other sterol and sterol precursors.

In a 12-week, double-blind, placebo-controlled study in 40 patients with primary hypercholesterolemia, ZOCOR reduced LDL-C by 50% at the recommended dose.
In a 4S, the effect of simvastatin with ZOCOR on total mortality was assessed in 5,444 patients with CHD and baseline total cholesterol of 212-302 mg/dL (5.5-7.8 mmol/L). In this multi-center, randomized, double-blind, placebo-controlled, study, patients were treated with standard care, including diet, and were given ZOCOR 20 mg daily (n=2,223) or placebo (n=2,223) for a median duration of 5.4 years. Over the course of the study, treatment with ZOCOR led to mean reductions in total-C, LDL-C and TG of 17%, 23%, and 10%, respectively; and a mean increase in HDL-C of 4%. ZOCOR significantly reduced the risk of mortality (Figure 1) by 30% (p=0.0003; 178 deaths in the ZOCOR group; 256 deaths in the placebo group). The risk of CHD mortality was significantly reduced by 42% (p=0.00001, 111 vs 166). There was no statistically significant difference between groups in non-cardiovascular mortality.

ZOCOR also significantly decreased the risk of having major coronary events (CHD mortality plus hospital-verified and silent non-fatal myocardial infarction [MI]) (Figure 2) by 34% (p=0.00001; 343 patients vs 627 patients with one or more events). The risk of having hospital-verified non-fatal MI was reduced by 35%. ZOCOR significantly reduced the risk for undergoing myocardial revascularization procedures (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) by 17% (p=0.00001; 282 patients vs 353 patients). Furthermore, ZOCOR significantly reduced the risk of fatal plus non-fatal cerebrovascular events (combined stroke and transient ischemic attack) by 28% (p=0.003; 76 events vs 102 events). ZOCOR reduced the risk of major coronary events by a similar extent across the age range of baseline patients (total and LDL cholesterol levels). The risk of mortality was significantly decreased in patients aged 60 years or age by 25% and 60 years of age by 17%. The risk of fatal MI was significantly decreased by 25% in patients aged 60 years of age by 25%. ZOCOR also significantly reduced the risk of CHD mortality in women aged 70 years by 20%. However, ZOCOR significantly decreased the risk of having major coronary events in women aged 60 years by 20%. ZOCOR significantly decreased the risk of having major coronary events in women aged 70 years by 25%.

Table: ZOCOR® (simvastatin)

<table>
<thead>
<tr>
<th>Column Number: 7824433</th>
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</table>
ZOCOR® (simvastatin)

who had matched angiographic projections at baseline, two and four years is presented below (Figures 3 and 4).

![Graph of Mean Lumen Diameter](image)

![Graph of Minimum Lumen Diameter](image)

**Endpoints:**

In clinical studies, simvastatin did not impair adrenal reserve or significantly reduce basal plasma cortisol concentration. Small reductions from baseline in basal plasma testosterone in men were observed in clinical studies with simvastatin, an effect also observed with other inhibitors of HMG-CoA reductase, and the bile acid sequestrant cholestyramine. There was no effect on plasma gonadotropin concentrations in placebo-controlled 12-week studies in men on simvastatin. In a study of 142 men on simvastatin and 143 on placebo, there was a significant increase in the mean plasma total testosterone concentration, with no effect on plasma luteinizing hormone (LH) concentration. These effects were not statistically significant in a group of 2,467 patients treated with simvastatin or placebo daily for a mean of 4 years, the evidence of male sexual function in the two treatment groups was not significantly different, but the influence of these factors on the cumulative risk of coronary events in men is uncertain, and the clinical importance of these observations is unknown.

ZOCOR® (simvastatin)

to measure total-C, HDL-C, and TG. For patients with TG less than 400 mg/dL (4.5 mmol/L), LDL-C can be estimated using the following equation:

\[ \text{LDL-C} = \text{Total-C} - (0.20 \times \text{TG} + \text{HDL-C}) \]

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 many hypertriglyceridemic patients, LDL-C may be low or normal despite elevated total-C. In such cases, ZOCOR® is not effective.

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 NCEP Treatment Guidelines are summarized below:

<table>
<thead>
<tr>
<th>LDL-Cholesterol mg/dL (mmol/L)</th>
<th>NCEP Treatment Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definite Atherosclerotic Disease</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td><strong>Two or More Other Risk Factors</strong>&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>YES</td>
<td>YES OR NO</td>
</tr>
</tbody>
</table>

1. Coronary artery disease or peripheral vascular disease, or symptomatic carotid artery disease.

2. Other risk factors for coronary artery disease (CHD) include: age (males > 45 years; females > 55 years); smoking; diabetes; family history of premature CHD; current cigarette smoking, hypertension, and hyperlipidemia. The CHD risk factor of HDL-C is < 50 mg/dL (1.3 mmol/L). Suggest one risk factor of HDL-C is > 60 mg/dL (1.6 mmol/L).

3. In CHD patients with LDL-C levels > 160 mg/dL, the physician should exercise clinical judgment in deciding whether or not to initiate drug therapy.

At the time of hospitalization for an acute coronary event, consideration can be given to initiating drug therapy at discharge if the LDL-C is > 130 mg/dL (3.4 mmol/L). (NCEP Treatment Guidelines, above).

Since the goal of treatment is to lower LDL-C, the NCEP recommends that LDL-C levels be used to monitor and assess treatment response. Only if LDL-C levels are not available should the total-C be used to monitor treatment response. ZOCOR® is indicated to reduce elevated LDL-C and TG levels in patients with type II a (hypercholesterolemia) or type IV (very high cholesterol levels with a familial history of hypercholesterolemia) and/or type V (mixed hyperlipidemia) hyperlipidemias, and those with LDL-C > 160 mg/dL (4.1 mmol/L).

**CONTRAINDICATIONS**

- Prolonged use of any component of simvastatin therapy may cause aplastic anemia or agranulocytosis. Use with caution in patients with rheumatoid arthritis.
- Use with caution in patients with severe liver or renal disease.
- Avoid use in patients with active liver disease or severe renal impairment (creatinine clearance < 30 mL/min).
- Use with caution in patients with active liver disease or severe renal impairment (creatinine clearance < 30 mL/min).
- Use with caution in patients with active liver disease or severe renal impairment (creatinine clearance < 30 mL/min).
diseases or other clinical signs or symptoms. There was no evidence of hypercholesterolemia.

In a 45-week clinical pharmacology study in clinical studies, the number of patients with more than one transaminase elevation (AST > 3X ULN or ALT > 3X ULN) or a measure of the study was significantly different between the simvastatin and placebo groups. (14.6% vs. 17.0%). Elevated transaminases resulted in discontinuation of treatment in the simvastatin group (n=5) and 5 in the placebo group (n=7). Of the 1,963 simvastatin treated patients to 44 with normal liver function tests (LFTs) at baseline, only 14 (0.4%) developed consecutive LFT elevations > 3X ULN and/or were discontinued due to transaminase elevations during the 4-year median follow-up of the study. Among these 14 patients, 5 initially developed these abnormalities within the first year. All of the patients in this study received a starting dose of 20 mg of simvastatin; 57% were titrated to 40 mg.

In 2 controlled clinical studies in 1,105 patients, the 12-month incidence of persistently elevated hepatic transaminase elevations without regard to drug relationship was 0.9% and 2.4% at the 40- and 80-mg dose, respectively. No patients developed persistent liver function abnormalities following the (initial 6 months of treatment at 40 mg.

It is recommended that liver function tests be performed before the initiation of treatment and periodically thereafter (e.g., semianually) for the first year of treatment or until one year after the last elevation in dose. Patients initiated to the 80-mg dose should receive an additional test at 3 months. Patients who develop increased transaminase levels should be evaluated to rule out other causes of liver injury. Therapy with simvastatin should be discontinued if liver function tests exceed normal limits after any dose change or if jaundice occurs.

The safety of simvastatin has been assessed in a variety of clinical studies involving a large number of patients treated for 1 to 12 months. In these studies, simvastatin was well tolerated. Adverse events in clinical studies were similar to those reported in the placebo group. Adverse events were generally mild or moderate in severity, and were reversible with discontinuation of simvastatin.

In a 96-week study involving 2000 patients, simvastatin was well tolerated. The most common adverse event was diarrhea. The incidence of diarrhea was similar in the simvastatin and placebo groups. In addition, there was no evidence of hypercholesterolemia.

In clinical studies, simvastatin was well tolerated. The most common adverse events were diarrhea and nasopharyngitis. The incidence of diarrhea was similar in the simvastatin and placebo groups. In addition, there was no evidence of hypercholesterolemia.

In a 96-week study involving 2000 patients, simvastatin was well tolerated. The most common adverse event was diarrhea. The incidence of diarrhea was similar in the simvastatin and placebo groups. In addition, there was no evidence of hypercholesterolemia.

In general, adverse events were similar to those reported with placebo. Adverse events were generally mild or moderate in severity and were reversible with discontinuation of simvastatin.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 12-week carcinogenicity study, mice were administered daily doses of simvastatin of 25, 50, and 100 mg/kg body weight, which resulted in mean plasma drug levels approximately 1.4 and 8 times higher than the mean human plasma drug levels, respectively (as total hydroxylic activity based on AUC after an 80-mg oral dose). Liver vacuolations were significantly increased in both males and females, and mid-dose males and high-dose females had increased vacuolations. There was a significant increase in the incidence of adenomas of the liver in females at higher drug levels and in males at mid-dose more than in controls. No evidence of a tumorigenic effect was observed at 75 mg/kg/day.

In a separate 97-week carcinogenicity study, rats were administered daily doses of simvastatin of 25, 50, and 100 mg/kg body weight, which resulted in mean plasma drug levels approximately 4 and 8 times higher than the mean human plasma drug levels, respectively (as total hydroxylic activity based on AUC after an 80-mg oral dose). Liver vacuolations were significantly increased in both males and females, and mid-dose males and high-dose females had increased vacuolations. There was a significant increase in the incidence of adenomas of the liver in females at higher drug levels and in males at mid-dose more than in controls. No evidence of a tumorigenic effect was observed at 75 mg/kg/day.

In a second 12-week carcinogenicity study, rats were administered daily doses of simvastatin of 25, 50, and 100 mg/kg body weight, which resulted in mean plasma drug levels approximately 1.4 and 8 times higher than the mean human plasma drug levels, respectively (as total hydroxylic activity based on AUC after an 80-mg oral dose). Liver vacuolations were significantly increased in both males and females, and mid-dose males and high-dose females had increased vacuolations. There was a significant increase in the incidence of adenomas of the liver in females at higher drug levels and in males at mid-dose more than in controls. No evidence of a tumorigenic effect was observed at 75 mg/kg/day.

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genetic material was noted in an in vitro alkaline elution assay using rat hepatocytes, a V-79 mammalian cell forward mutation study, an in vitro chromosomal aberration study in CHO cells, or an in vivo chromosomal aberration assay in mouse bone marrow.

There was decreased fertility in male rats treated with simvastatin for 34 weeks at 25 mg/kg body weight (4 times the maximum human exposure level, based on AUC in patients receiving 80 mg/day); however, this effect was not observed during a subsequent fertility study in which simvastatin was administered at the same dose level to male rats for 11 weeks, (the entire cycle of spermatogenesis including epididymal maturation). No microscopic changes were observed in the testes of rats from either study. At 180 mg/kg/day, (which produces exposure levels 32 times higher than those in humans taking 80 mg/day based on surface area, mg/m²), seminiferous tubule degeneration (apoptosis and loss of spermatogenic epithelium) was observed. In dogs, there was drug-related testicular atrophy, decreased spermatogenesis, spermatogenic degeneration and giant cell formation at 30 mg/kg/day, (approximately 2 times the human exposure, based on AUC at 80 mg/day). The clinical significance of these findings is unclear.

Pregnancy

Pregnancy Category A

See CONTRAINDICATIONS.

Simvastatin was not teratogenic in rats or at lower doses of 5 mg/kg/day or rabbits at doses up to 10 mg/kg/day. No effects on fetal development or skeletal malformations were observed in rats and rabbits. Fetal weight and length were lower in rats exposed to simvastatin in the gestation period. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

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.

Pediatric Use

Safety and effectiveness in children have not been established.
serious adverse reactions in nursing infants. Women taking simvastatin should not nurse their infants (see CONTRAINDICATIONS).

Pediatric Use
Safety and effectiveness in pediatric patients have not been established because pediatric patients 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 pediatric patients with simvastatin is not recommended at this time.

ADVERSE REACTIONS
In the pre-marketing controlled clinical studies and their open extensions, 12,423 patients with a mean duration of follow-up of approximately 18 months, 1.4% of patients were discontinued due to adverse experiences attributable to ZOCOR. Adverse reactions have usually been mild and transient. ZOCOR has been evaluated for serious adverse reactions in more than 21,000 patients and is generally well tolerated.

Clinical Adverse Experiences
Adverse experiences occurring at an incidence of 1 percent or greater in patients treated with ZOCOR, regardless of causality, in controlled clinical studies are shown in the table below.

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>ZOCOR (N=9,000)</th>
<th>Placebo (N=1,517)</th>
<th>Cholestyramine (N=1,517)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body as a Whole</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>32 (4%)</td>
<td>22 (4%)</td>
<td>10 (7%)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>8 (1%)</td>
<td>5 (1%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>23 (3%)</td>
<td>13 (2%)</td>
<td>11 (2%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1.9 (0.8%)</td>
<td>1.0 (0.6%)</td>
<td>1.0 (0.6%)</td>
</tr>
<tr>
<td>Flatulence</td>
<td>1.0 (0.4%)</td>
<td>1.0 (0.4%)</td>
<td>1.0 (0.4%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>1.3 (0.4%)</td>
<td>1.5 (0.5%)</td>
<td>1.5 (0.5%)</td>
</tr>
<tr>
<td>Psychiatric</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>1.5 (0.4%)</td>
<td>1.1 (0.3%)</td>
<td>1.1 (0.3%)</td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td>21 (1.1%)</td>
<td>19 (1.5%)</td>
<td>19 (1.5%)</td>
</tr>
</tbody>
</table>
ZOCOR® (simvastatin)

Scandinavian Simvastatin Survival Study
Clinical Adverse Experiences

In 4S (see CLINICAL PHARMACOLOGY, Clinical Studies) involving 4,444 patients treated with 20-40 mg/day of ZOCOR (n=2,221) or placebo (n=2,223), the safety and tolerability profiles were comparable between groups over the median 5.4 years of the study. The clinical adverse experiences reported as possibly, probably, or definitely drug-related in ≥0.5% in either treatment group are shown in the table below:

<table>
<thead>
<tr>
<th>Drug-Related Clinical Adverse Experiences in 4S (Incidence ≥0.5 Percent or Greater)</th>
<th>ZOCOR (n = 2,221) %</th>
<th>Placebo (n = 2,223) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body as a Whole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0.6</td>
<td>0.3</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>0.6</td>
<td>0.5</td>
</tr>
<tr>
<td>Flatulence</td>
<td>0.9</td>
<td>0.7</td>
</tr>
<tr>
<td>Nausea</td>
<td>0.4</td>
<td>0.6</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>1.2</td>
<td>1.3</td>
</tr>
<tr>
<td>Skin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythema</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>Pruritus</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>Rash</td>
<td>0.4</td>
<td>0.6</td>
</tr>
<tr>
<td>Special Sensory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tinnitus</td>
<td>0.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>

The following effects have been reported with drugs in this class. Not all the effects listed below have necessarily been reported with ZOCOR, but they are the types of reactions that have been observed with other HMG-CoA reductase inhibitors: digestive symptoms, myalgia, myopathy, rhabdomyolysis, hyperuricemia, angina pectoris, muscle pain/myalgia, nausea, vomiting, diarrhea, constipation, flatulence, liver abnormalities, pneumonia, interstitial lung disease, pancreatitis, rash, edema, fluid retention, asthenia, pruritus, alopecia, breast pain, breast enlargement, breast tenderness, hot flashes, decreased libido, dyspnea, nervousness, depression, abdominal pain, elevated liver enzymes, hyperglycemia, diabetes mellitus, hyperuricemia, gout, peripheral neuritis, peripheral neuropathy, peripheral sensory symptoms, increased ALT, AST, and alkaline phosphatase, positive ANA, eosinophilia, headaches, and visual disorders. They have also been associated with other lipid lowering treatments (e.g., LDL apheresis).

ZOCOR® (simvastatin)
with cyclosporine, fibrates or niacin, and for those with severe renal insufficiency.

The recommended dose range is 5-80 mg/day as a single dose in the evening. Doses should be individualized according to baseline LDL-C levels, the recommended goal of therapy (see NCEP Treatment Guidelines), and the patient's response. Adjustments of dosage should be made at intervals of 4 weeks or more.

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

Dose in Patients with Homozygous Familial
Hypercholesterolemia

Based on the results of a controlled clinical study, the recommended dosage for patients with homozygous familial hypercholesterolemia is ZOCOR 40 mg/day in the evening or 80 mg/day in divided doses of 20 mg. 20 mg, and an evening dose of 40 mg. ZOCOR should be used as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis). In these patients or if such treatments are unavailable.

General Recommendations

In the elderly, maximum reductions in LDL-C may be achieved with daily doses of 20 mg of ZOCOR or less.

In patients taking cyclosporine concomitantly with simvastatin see WARNINGS, Skeletal Muscle. Therapy should begin with 5 mg of ZOCOR and be escalated to 10 mg/day.

Concomitant Lipid-Lowering Therapy

ZOCOR is effective alone or when used concomitantly with bile-acid sequestrants. Use of ZOCOR with other lipid-lowering agents should generally be avoided. However, if ZOCOR is used in combination with a fibrate or niacin, the dose of ZOCOR should not exceed 20 mg/day. See WARNINGS, Skeletal Muscle.

Dose in Patients with Renal Insufficiency

Because ZOCOR does not undergo significant renal excretion, modification of dosage should not be necessary in patients with mild to moderate renal insufficiency. However, caution should be exercised when ZOCOR is administered to patients with severe renal insufficiency (creatinine clearance of ≤30 mL/min) or end-stage renal disease on dialysis. See WARNINGS, Pharmocokinetics and WARNINGS, Skeletal Muscle.

HOW SUPPLIED

R 8965 Tablets ZOCOR 5 mg; uncoated, 10's/box, 25's/box, 200's/box and ZOCOR 10 mg; uncoated, 10's/box, 25's/box, 200's/box

R 8966 Tablets ZOCOR 20 mg; uncoated, 10's/box, 25's/box, 200's/box and ZOCOR 40 mg; uncoated, 10's/box, 25's/box, 200's/box

NDC 0003-0270-10 Tablets 5 mg; uncoated, 10's/box, 25's/box, 200's/box
NDC 0003-0271-10 Tablets 10 mg; uncoated, 10's/box, 25's/box, 200's/box
NDC 0003-0272-10 Tablets 20 mg; uncoated, 10's/box, 25's/box, 200's/box
APPLICATION NUMBER:
19-766/S035

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS
MEDICAL OFFICER'S REVIEW OF SPECIAL SUPPLEMENT-CHANGES BEING EFFECTED

NDA: 19-766/S-035                  SUBMITTED: 2/16/99
SPONSOR: MERCK RESEARCH LAB.       RECEIVED: 2/17/99
DRUG: ZOCOR (Simvastatin)          REVIEWED: 5/6/99

I. RESUMED:

Three cases of myopathy have been reported in patients on simvastatin and HIV protease inhibitors. The basis of this interaction is due to cytochrome P450 isoform 3A4 substrate competition between protease inhibitors and simvastatin. The greatly increased plasma concentration of simvastatin may result in myopathy (rhabdomyolysis) in sensitive patients.

II. Proposed Labeling Revision:

Add the phrase "HIV protease inhibitors" to the drugs list in WARNINGS, Skeletal Muscles, Myopathy caused by drug interaction, and in PRECAUTIONS, Drug Interactions.

III. Evaluation:

The proposed revisions in labeling are acceptable.

IV. Recommendations:

This Supplement (CBE) is approved.

S.W. Shen, M.D.
Medical Officer, HFD-510

CC:
Original NDA
HFD-510 Files
HFD-510-SWSHEN
HFD-510-SIMONEAU
NDA 19-766/S-035

Merck Research Laboratories
Sumneytown Pike, P.O. Box 4 BLA-20
West Point, PA 19486

Attention: Charles L. Hyman, M.D.
Director, Regulatory Affairs

Dear Dr. Hyman:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Zocor *(Simvastatin)

NDA Number: 19-766

Supplement Number: S-035

Date of Supplement: February 16, 1999

Date of Receipt: February 17, 1999

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on April 18, 1999, in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Attention: Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

[Signature]

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research
cc:
   Original NDA 19-766/S-035
   HFD-510/Div. Files
   HFD-510/CSO/M. Simoneau

filename: C:\DATA\WPFILES\19766ACK.

SUPPLEMENT ACKNOWLEDGEMENT /CBE
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:

NDA 19-766: ZOCOR™ (Simvastatin)  
SPECIAL SUPPLEMENT - CHANGES BEING EFFECTED

Pursuant to Section 505(b) of the Food Drug and Cosmetic Act and in accordance with 21 CFR 314.70 (c)(2), we submit a supplement to NDA 19-766.

As indicated on the attached Form FDA 356h, this supplemental application provides for changes in the Labeling Section of the approved New Drug Application for ZOCOR™.

The circular (#7825433) has been revised to add the phrase “HIV protease inhibitors” to the drugs list in WARNINGS, Skeletal Muscles, Myopathy caused by drug interaction, and in PRECAUTIONS, Drug Interactions.

Also, for consistency in presentation, the four tables occurring in this circular are editorially reformatted to one style. Where appropriate, titles are added and horizontal black lines are added to set apart the table form the running text. These editorial revisions are found in CLINICAL PHARMACOLOGY, Clinical Studies; INDICATIONS AND USAGE, General Recommendations; and ADVERSE REACTIONS.

The following are attached to this supplement:

- One (1) copy of the Summary of Revisions
- One (1) copy of the Annotated Circular illustrating the revisions
- Twenty (20) mounted copies of the Printed Package Circular #7825433

The changes will become effective on or about July 1, 1999 and will apply to all packages of ZOCOR™ distributed from the company’s manufacturing facilities at West Point, PA.
Please note that this circular replaces circular #7825431.

In accordance with the Food and Drug Administration Modernization Act of 1997, as indicated in the attached Form 3397, no user fee is required for this supplemental application.

As required by Section 306(k)(1) of the Generic Enforcement Act [21 U.S.C. 335a(k)(1)], we hereby certify that, in connection with this application, Merck & Co., Inc. did not and will not use in any capacity the services of any person debarred under subsections 306(a) or (b) of the Act.

Merck is requesting a categorical exclusion from the requirements to prepare an Environmental Assessment under 21 CFR §25.31(a). The supplement meets the requirements of a categorical exclusion under 21 CFR §25.31(a) because it will not increase the use of the active moiety, (Active Ingredient). To the best of the firm’s knowledge no extraordinary circumstances exist in regards to this action.

We consider the filing of this Supplemental New Drug Application to be a confidential matter, and request the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Please direct questions or need for additional information to Charles L. Hyman, M.D. (610/397-2850) or, in my absence, Robert E. Silverman, M.D., Ph.D. (610/397-2944).

Sincerely,

[Signature]

Charles L. Hyman, M.D.
Director
Regulatory Affairs

Attachments

Federal Express
Q:

REVIEWED COMPLETED

AP 9/15/99

CSO ACTION:
LETTER N.A.I. MEMO

N/A 9/16/99

CSO INITIALS DATE
DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

1. APPLICANT'S NAME AND ADDRESS
Merck & Co., Inc.
Sunnystown Pike, BLA-10
P. O. Box 4
West Point, PA 19486

3. PRODUCT NAME
ZOCOR (Simvastatin)

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?
IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE
AND SIGN THIS FORM.

IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

☐ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUMMITTED BY
REFERENCE TO

(Application No. containing the DATA).

2. TELEPHONE NUMBER (Include Area Code)
(610) 397-2383

5. USER FEE I.D. NUMBER

6. LICENSE NUMBER / NDA NUMBER
N019766

7. 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 UNDER SECTION 505 OF THE FEDERAL
FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/82
(Self Explanatory)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN
EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food,
Drug, and Cosmetic Act
(See Item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL
GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED
COMMERCIALY
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See Item 7, reverse side before checking box.)

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT
QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of
the Federal Food, Drug, and Cosmetic Act
(See Item 7, reverse side before checking box.)

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR
TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN APPLICATION FOR A BIOLOGICAL PRODUCT
FOR FURTHER MANUFACTURING USE ONLY

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT
LICENSED UNDER SECTION 351 OF THE PHS ACT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL
APPLICATION LICENSED BEFORE 8/1/82

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

☐ YES ☐ NO
(See reverse side if answered YES)

A completed form must be signed and accompany each new drug or biologic product application and each new
supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewer
instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information.
Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0297)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not
required to respond to, a collection of information unless it
displays a currently valid OMB control number.

Please DO NOT RETURN this form to this address.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE
Bonnie J. Goldmann, M.D.
Vice President, Domestic Liaison
Regulatory Affairs

FORM FDA 3397 (5/98)