

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 19-766/S040

MEDICAL REVIEW(S)

APR 18 2000

NDA # 19-766/S-040

ZOCOR (simvastatin) tablets

Merck

Drug class: Lipid altering; HMG-CoA reductase inhibitor

Proposed changes in labeling: To amend Dosage and Administration to add 40 mg daily as an optional starting dose in addition to 10 and 20 mg daily

Date of submission: June 30, 1999

Date of review: April 18, 2000

Medical Officer and Medical Team Leader review of supplemental NDA

Background

Simvastatin is a member of the HMG-CoA reductase inhibitor class (HMGR) of lipid altering drugs. By inhibiting HMG-CoA reductase, the rate-limiting enzyme in cholesterol biosynthesis, these drugs deplete hepatic intracellular cholesterol pools leading to a de-repression of expression of the LDL-receptor gene. Increased synthesis and surface expression of LDL-receptors on hepatocytes leads to increased clearance of LDL particles from the plasma and, ultimately, in reduced steady-state levels of LDL-C in plasma.

Overwhelming evidence from epidemiological studies, animal models of atherosclerosis, and animal and human pathological studies supports elevated LDL-C as a major risk factor for (and causative factor in) atherosclerosis. Clinical trials of cholesterol lowering provide irrefutable support that a variety of interventions to lower LDL-C lower risk for atherosclerosis-related clinical events.

Simvastatin is marketed in dosage strengths of 5 mg to 80 mg. Treatment with 80 mg daily resulted in clinical trials in a 47% mean decrease in LDL-C from baseline in patients with primary hypercholesterolemia and mixed dyslipidemia (Fredrickson Types IIa and IIb). In addition, simvastatin as well as other members of the class induce reductions in TG and increases in HDL-C in a high percentage of patients, though these changes are much more variable than those in LDL-C levels and of unknown independent clinical significance.

There is no evidence for differential safety of simvastatin across the dyslipidemic phenotypes for which it is indicated. As for other statins, simvastatin use has been associated with dose related increases in the incidence of persistent transaminase elevations to > 3 X ULN. Current labeling for simvastatin states a 2.1% 12-month incidence of such events across two large clinical trials in patients treated with 80 mg daily. As with other members of the class, in the vast majority of instances, these elevations are not associated with jaundice or hyperbilirubinemia. All evidence suggests that statins are not significant hepatotoxins.

The most serious adverse event associated with statin therapy is myopathy. This is an extremely rare event, occurring at a rate of approximately 1:10,000 patients treated for 1 year and apparently related to systemic levels of active drug. The rarity of these events

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40 mg alternative starting dose

does not permit conclusions as to dose-relatedness. Many if not most reported cases of serious myopathy and rhabdomyolysis occur in the context of factors predisposing to increased levels of active drug in the systemic circulation. These factors include age, concomitant major illness, and concomitant use of drugs that increase the bioavailability of the culprit statin by inhibiting metabolic clearance. This has been most frequently observed with inhibitors of CYP 3A4 used in conjunction with statins metabolized by CYP 3A4 (simvastatin, lovastatin, atorvastatin, cerivastatin).

Simvastatin has been studied in numerous controlled clinical trials, including simple lipid-altering studies, studies of angiographic progression of atherosclerotic disease, and in a large endpoint trial, 4S (Scandinavian Simvastatin Survival Study). This was a double-blind, randomized, placebo-controlled, multicenter study in which 4444 patients were treated for an average of 5 years with either placebo or simvastatin (1:1). Approximately one-third of the 2222 patients on simvastatin were treated with 40 mg daily from the 6-month visit onward. The trial found a significant reduction in death due to all causes, as well as coronary death, all cardiovascular death, non-fatal MI, total stroke, and coronary revascularization procedures in the simvastatin-treated patients relative to placebo.

There was one case of myopathy in 4S in a patient taking 20 mg simvastatin. The incidence of persistent marked ($>3X$ ULN) hepatic transaminase elevations was not significantly different across the two treatment groups ($<1\%$ in both), and the rate of discontinuation due to LFT abnormalities was likewise similar between the two treatment groups ($<1\%$).

Simvastatin was approved for U.S. marketing in 1991. The original dosage strengths were 5 mg, 10 mg, 20 mg, and 40 mg. According to the current label, the mean LDL-C reductions from baseline across these doses are 26%, 30%, 38%, and 41%, respectively. The original labeling for simvastatin, and for the other members of the class, recommended starting with a low dose and up-titrating according to LDL-C response and goal of therapy. This recommendation was, to some degree, based upon the principle that lower doses were safer and that tolerance should be established at lower doses before challenging the patient with higher doses. In addition, the guidelines for the treatment of hypercholesterolemia did not establish the low goals that are now recommended (e.g., LDL-C < 100 mg/dL for all patients with CHD). Since the approval of ZOCOR, not only have the goals been adjusted downward, but also clinical trials have demonstrated benefits of cholesterol lowering that, arguably, increase with increasing reductions from baseline. Furthermore, a huge body of experience with these agents in clinical trials and in open market use speaks to their general safety and tolerability across approved doses and across different populations and at-risk patients. It is also notable that the lowest marketed dose of atorvastatin (10 mg daily), marketed since early 1997, effects a mean 39% reduction in LDL-C from baseline. Finally, there is ample evidence of poor compliance with lipid lowering regimens (treatment of a chronic asymptomatic disease) with less than 50% of patients started on treatment still taking these medications after 1 year. This, in conjunction with the fact, cited by the sponsor, that physicians rarely titrate these drugs past the starting dose, leads the sponsor to the proposal that the 40 mg

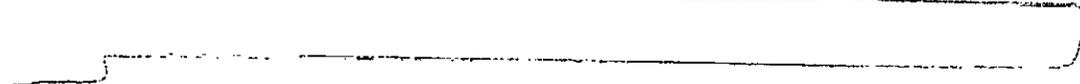
dose be recommended for patients requiring a greater than 45% LDL-C reduction from baseline. The following reviews the information provided in support of the proposed changes.

Proposed changes to labeling

All proposed changes are in the Dosage and Administration section. Although the recommendation that 20 mg daily be the usual starting dose is maintained, the sponsor proposes adding the following:

Patients who require a large reduction in LDL-C (more than 45%) may be started at 40 mg/day in the evening.

In addition to editorial revisions, the sponsor proposes to delete the following statement:



Data submitted in support of the proposed changes to labeling

The current labeling recommends 20 mg daily in the evening as the usual starting dose of simvastatin. Patients requiring only a "moderate" reduction in LDL-C from baseline may be started on a dose of 10 mg daily. Dose in patients taking cyclosporine and concomitant fibrates or niacin is not to exceed 10 mg daily because of the risk of myopathy with such combinations.

The sponsor has crafted a 3-pronged argument in favor of the proposed labeling. First, the submission contains results of analyses showing the percentage of U.S. patients age 20 or older and eligible for lipid-lowering therapy who would reach NCEP goals at currently recommended doses of simvastatin. This is based upon assumptions of a 5% LDL-C reduction by diet, and reductions of 28, 35, 41, and 47% with 10, 20, 40, and 80 mg simvastatin daily, respectively. The table is reproduced below.

Percentage of U.S. adults > 20 years achieving NCEP target LDL-C levels across simvastatin dose range by risk category							
Risk group	Percent of U.S. population	Treatment threshold/goal LDL-C (mg/dL)	Percent with LDL-C above threshold	Percentage achieving target LDL-C level			
				Simvastatin dose			
				10 mg	20 mg	40 mg	80 mg
CHD	7	130/100	46	27	45	61	75
≥ 2 RF*	27	160/130	31	50	69	83	92
< 2 RF	66	190/160	4	73	88	95	98

*risk factors for CHD

The additional ~15% of patients across all three risk strata who can be expected to achieve target LDL-C levels on 40 mg versus 20 mg simvastatin represents a substantial number of at-risk patients. Assuming that this can be accomplished safely, the population benefit of such a difference is significant.

By way of complementing the above data, evidence is presented from the published literature that speaks to the low percentage of patients eligible for lipid lowering therapy reaching goal and to the infrequency of diligent titration of lipid altering therapy to reach treatment goals.

In the second part of the argument, data from simvastatin clinical trials are presented showing the percentiles of the treatment populations by % LDL-C reduction from baseline. Notable from the sponsor's table, not reproduced here, is the fact that at the 20 mg dose, only about 20% of the patients achieved at least a 45% reduction from baseline, whereas at 40 mg, nearly 40% of patients achieved at least a 45% reduction in LDL-C from baseline. This information, in conjunction with that derived from the table above, suggests that 40 mg is a significantly more efficacious dose of simvastatin, from the standpoint of optimal LDL-C lowering, than is 20 mg.

Finally, the submission includes a lengthy discussion of the safety experience with ZOCOR with particular reference to the 40 mg dose. In addition to the completed NDA trials and 4S, reference is made to published data from the Heart Protection Study (HPS), a megatrial in which more than 20,000 patients at high risk of CHD up to 80 years of age have been randomized to simvastatin 40 mg or placebo. The published safety data reflect a mean 2 years of exposure.

The experience in this trial is consistent with that in other trials of simvastatin. During the run-in period (4 weeks placebo followed by 6 weeks simvastatin 40 mg), two of 32,145 patients developed myopathy. As of the data wrap for the publication, two of the 10,269 patients randomized to simvastatin 40 mg and 2 of the 10,267 patients randomized to placebo had developed myopathy. One of the 2 placebo patients developed frank rhabdomyolysis following coronary revascularization, apparently precipitated by thrombolytic therapy with streptokinase. The other placebo patient was hypothyroid.

According to the sponsor, as of March 1999, Merck has received 3 additional reports of myopathy in patients randomized to simvastatin, bringing the total in the simvastatin group to 5. Thus, after a median duration of therapy of approximately 3 years, the incidence of myopathy in the simvastatin group is 0.05%.

With regard to hepatic effects of simvastatin, the Heart Protection Study publication reports thirty-nine patients randomized to simvastatin and 32 to placebo with asymptomatic elevations in ALT to $> 3 \times$ ULN. In 1 of the patients in the simvastatin group, ALT values remained abnormal after stopping simvastatin, and approximately 1 year later the patient developed clinical hepatitis. Viral serology was negative. The patient recovered although ALT values remained abnormal.

Summary and conclusions

The proposal simply adds 40 mg as an optional starting dose of simvastatin for those requiring more robust reductions in LDL-C from baseline. The 20 mg dose remains as

the usual recommended starting dose. The sponsor has proposed the deletion of the recommendation for the 10 mg starting dose for those patients requiring only "moderate" reductions in LDL-C from baseline to goal.

The dose-response in terms of LDL-C lowering with simvastatin has been well characterized and simvastatin has been so labeled. As for other members of this class, there is an average incremental 6-7% LDL-C lowering from baseline with successive doubling of the dose of drug. The effect of simvastatin (% change from baseline) and other statins on LDL-C lowering is not affected by baseline LDL-C. Evidence from lipid lowering endpoint trials as well as from epidemiological studies suggests a graded and continuous relationship between LDL-C and risk for CHD. Thus, by and large, assuming safe drugs, lower is probably better. The sponsor has presented data showing the dose-related incremental efficacy of simvastatin as measured by percentiles of treated patients achieving various degrees of LDL-C lowering by dose of drug and as measured by the percent of patients by CHD risk category reaching LDL-C targets by dose of drug. This, in conjunction with the large database on simvastatin safety and tolerability reaffirmed by the interim data from the ongoing Heart Protection Study, lends further rationale to the proposed change to the recommending starting dose of simvastatin.

Labeling

The proposed changes are all acceptable.

Recommendation

This supplemental NDA may be approved.

David G. Orloff, M.D.
Deputy Director/Medical Team Ldr
DMEDP/ODE-II/CDER/FDA

Recommendation code: AP

ISI 4-18-00

CC:
NDA 19-766 Arch
HFD-510

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The clinical studies essential to the approval of this sNDA were completed prior to the date of submission. Therefore, no safety update is needed.

David G. Orloff, M.D.

/S/ 4-27-00

**APPEARS THIS WAY
ON ORIGINAL**