CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER for: 020702, S018

MEDICAL REVIEW(S)

NDA 20-702/S-018
Lipitor (atorvastatin calcium) tablets
Parke-Davis
Therapeutic class: lipid altering
Date of submission: March 3, 1999
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Medical Team Leader review of sNDA (serves also as primary medical officer review)

Proposed labeling changes to add HDL-C raising to Indications

Introduction
The role of cholesterol excess in atherosclerosis is well established based upon epidemiologic data, human and animal disease models, pathological studies, and *in vitro* experimentation.

Cholesterol is carried in the plasma in lipoproteins which serve as the transport and delivery machinery for TG used for metabolic fuel or stored in adipose tissue, and for cholesterol for incorporation into cell membranes, and as a starting material for sterol synthesis. Lipoproteins are synthesized primarily in the liver, and post-prandially by the small intestine.

Increased risk of atherosclerosis is conferred, based on epidemiologic studies, by elevations in total cholesterol, LDL-C, TG, and by low HDL-C. Atherogenic lipoproteins include LDL-C (especially small, dense species), VLDL (especially post-prandial chylomicron remnants), IDL (as occurs in dysbetalipoproteinemia), and Lp(a). The atherogenicity of lipoproteins is a function of particle size, apoprotein and lipid composition, residence time in the plasma, all of which determine the propensity to traverse the arterial endothelium, to bind to the proteoglycan matrix of the arterial wall, to be ingested by macrophages, and to be oxidized by macrophage peroxides, a cycle, that repeated, eventuates in arterial injury and dysfunction. Finally, all the above is further modulated by the presence of certain non-lipid factors, as hypertension, diabetes, and smoking. Suffice it to say that atherosclerosis is more than just a disease associated with high LDL-C. There is ample evidence for a role for certain species of cholesterol-enriched, TG-rich lipoproteins in atherogenesis as well.

As mentioned above, an inverse association between HDL-C levels and cardiovascular risk has been observed in numerous cohort studies. Indeed, the most common single lipid abnormality in patients with CAD before the age of 60 years is low HDL-C with accompanying elevated TG in approximately 40% of these patients. By contrast, TC and LDL-C are actually poor predictors of risk except when extremely high. In the Framingham cohort, for the first 26 years of follow up, there was a 90% overlap in the range of TC 150-300 mg/dL between patients with and without coronary disease manifest during that period. Indeed, 35% of the new onset CHD occurred in patients with TC under 200 mg/dL.

The mechanism by which elevated HDL-C ameliorates CHD risk is proposed to be by the process of reverse cholesterol transport. According to this hypothesis, nascent HDL particles can avidly take up cholesterol from lipid laden arterial plaques, and in the proper metabolic environment, can transport cholesterol ester to the liver for disposal.

Finally, while HDL-C level appears inversely correlated with risk in large series, elevated HDL-C is not always protective. One experiment of nature, cholesterol ester transfer protein (CETP) deficiency, leads to very high levels of HDL-C and in some kindreds to accelerated atherosclerosis.

Interventional trials of diet, surgery (ileal bypass), bile acid binding resins, fibrates, niacin, and statins, have all shown benefit with cholesterol lowering in terms of coronary and cardiovascular morbidity and mortality. The primary lipid response analysis for these trials has been change from baseline in LDL-C. Indeed, however, in the patients studied, with elevations in TC, LDL-C, with or without elevated TG and low HDL-C, the effect of active intervention has been on the panoply of lipids and lipoproteins. We currently have no drugs that render isolated changes in single lipid fractions or in single lipoprotein species, and thus have minimal data on the independent effects of changes in TG or HDL-C on outcomes in interventional trials. Of currently used agents, fibrates and niacin tend to have relatively minor effects on LDL-C levels, affecting predominantly levels of TG and HDL-C. By contrast, statins have their major impact on LDL-C levels, with generally smaller effects on TG and HDL-C.

With regard to mechanisms of action, statins and resins have their primary metabolic effect to increase the clearance of apo B-containing lipoproteins (including LDL, VLDL) from the circulation by increasing the expression of LDL receptors in the liver. Statins have a secondary effect to reduce the synthesis of these lipoproteins in the liver. As such, statins lower LDL-C, variably decrease TG levels, and variably increase HDL-C levels. Finally, it is well known that the effect of statins on TG levels depends upon baseline TG, with a greater reduction from baseline and per degree of LDL-C lowering in patients with higher baseline TG levels. Because of the metabolic interrelationship between TG and HDL-C, it has also been observed that HDL-C response to statins is a function of baseline TG and thus of baseline HDL-C.

Fibrates, by contrast, have little effect on LDL-C levels, rather have a predominant effect to lower TG and to raise HDL-C. These drugs act through peroxisome proliferator activator receptors (nuclear transcription factors) and affect the expression of a number of genes involved in lipoprotein and glucose metabolism.

The mechanism of action of niacin as a lipid altering agent is not well understood. Niacin has pleiotropic effects on lipoprotein metabolism including inhibition of release of free fatty acids from adipose tissue, increased lipoprotein lipase activity, and decreased rate of synthesis of hepatic VLDL. As such, it lowers LDL-C, TG, and raises HDL. In addition, niacin is the only available lipid altering agent that lowers levels of Lp(a), an

LDL-like particle that is independently associated with increased risk of atherosclerotic disease.

Endpoint studies in patients with primary hypercholesterolemia and mixed dyslipidemia (Fredrickson Types IIa and IIb) have been conducted with drugs across the currently used classes, including cholestyramine, niacin, gemfibrozil, clofibrate, lovastatin, pravastatin, and simvastatin. The salutary effects of lipid altering (event reduction) have been clearly demonstrated and seem to hold across age, sex, and risk-factor subgroups. In all of the these trials, the lipid effects have included, variably in magnitude, reductions in total and LDL-C, reductions in TG, and increases in HDL-C. Strictly speaking, attribution of clinical benefit to a single lipid alteration is not possible. The drugs produce a panoply of quantitative and qualitative changes in plasma lipids and it is reasonable to conclude that the drugs' lipid effects, *in toto*, are responsible for the reduction in clinical events. It is notable that in the large-scale statin trials, with now five completed and published, the most marked lipid effect is on LDL-C, with mean changes from baseline ranging, across the studies, from –25 to –35%. Needless to say, in these studies, the change in LDL-C has dwarfed that in HDL-C, and thus the clinical benefit seen has been largely attributed to the former. By contrast, in the niacin and fibrate trials, the changes in LDL-C have been much more modest, and, at least in theory, may not have dominated the clinical benefit.

In the recently completed VA-HIT (HDL Intervention Trial) study, patients with average LDL-C levels, TG $\leq$ 300, and HDL-C $\leq$ 40 were treated with either placebo or gemfibrozil and followed for a mean of 5.1 years. Clinical benefit in the gemfibrozil-treated group was associated with mean changes relative to placebo in plasma lipids of +4% in LDL-C, +7% in HDL-C, and –31% in TG. Again, there was not an isolated HDL effect of active treatment. Further analyses will be needed to determine if these patients truly had isolated low HDL-C as their sole lipid risk or whether they were at risk also because of atherogenic LDLs and/or TG-rich lipoproteins, this triad being the dyslipidemia of Syndrome X , or the metabolic syndrome. It must be emphasized that at this point, this study does not validate HDL-raising as an independent surrogate for clinical benefit.

The approach to labeling statins with regard to HDL-raising efficacy takes into account the following facts: 1) increases in HDL of variable magnitude are seen in a large percentage of patients treated with statins, 2) however, HDL-raising is not known to confer independent clinical benefit. Therefore, the inclusion of HDL data in labeling is merely intended to provide information for prescribers who might be interested in such an effect. The changes in HDL seen with one or another statin is one aspect of the overall effect of the drug on lipoprotein metabolism, and, as such, is information pertinent to labeling. A similar rationale may be applied to labeling nicotinic acid containing products with regard to HDL raising. As stated above, the independent effect of raising HDL-C with niacin on atherosclerosis risk has not been established. However, to the extent that niacin treatment has been of demonstrable clinical benefit in the Coronary Drug Project as well as in the two angiographic trials (CLAS, FATS) and to the extent that increases in HDL-C of variable magnitude are a consistent finding in niacin

treated individuals, the inclusion of HDL data in labeling is pertinent to the safe and effective use of the drugs. For both statins and niacin, the label must include a disclaimer to the effect that "the independent effect of raising HDL-C with (name of drug) has not been determined.

The current application proposes to add HDL raising in patients with Fredrickson types 2a and 2b to the Indications section of the Lipitor label. The data presented in support of the change are from some 24 clinical trials (all but 4 previously submitted to the NDA). This is termed by the sponsor the atorvastatin cumulative integrated database (CID).

Data sources and methods

The database employed for this application was derived by culling patients with Fredrickson Types IIa and IIb hyperlipoproteinemia across 24 studies completed as of July 8, 1998. Fredrickson Type II HLP was defined as LDL-C $\geq$ 135 mg/dL with or without hypertriglyceridemia. Patients were distributed as follows:

Atorvastatin (all doses)	2451
Pravastatin	171
Simvastatin	368
Placebo	250

Values employed in the analyses were from the first or only time point of interest in the study. Patients enrolled in forced titration studies contributed data only for the first dose of drug they received in the study.

For the current submission, Type II HLP was defined as baseline LDL-C $\geq$ 135 mg/dL. Since the enrollment criteria for the original studies excluded patients with marked hypertriglyceridemia, only the LDL-C criterion is needed for the current analysis.

Results from the cumulative integrated database

Mean percent change from baseline in HDL-C by treatment group in the pooled database

	Placebo N=250	Atorva 10 N=1871	Atorva 20 N=147	Atorva 40 N=115	Atorva 80 N=318	Prava 20 N=171	Simva 40 N=368
Baseline mean	49	48	48	48	46	50	44
Mean % change	1.0	6.7	8.2	8.6	7.0	5.8	7.6

Median (25^{th}, 75^{th} percentiles) for percent change from baseline in plasma lipids in pooled database

		Median (25^{th}, 75^{th} percentile) % change from baseline		
	N	LDL-C	HDL-C	TG
Atorva 10	1871	-38 (-44, -30)	6.4 (-1.4, 14)	-21 (-35, -4.4)
Atorva 20	147	-48 (-52, -37)	8.7 (0, 17)	-25 (-38, -4.2)

Atorva 20	147	-48 (-52, -37)	8.7 (0, 17)	-25 (-38, -4.2)
Atorva 40	115	-48 (-58, -41)	7.8 (0, 16)	-27 (-40, -12)
Atorva 80	318	-55 (-61, -47)	5.1 (-2.7, 15)	-34 (-46, -20)

Ranges of baseline means across treatment groups were, for HDL-C and TG, 46-48 mg/dL and 167-187 mg/dL, respectively.

The data show that modest increases in HDL-C are seen in the majority of patients with Type IIa and IIb treated with atorvastatin in controlled clinical trials.

Discussion

The sponsor has conducted analyses of the lipid responses among patients with Fredrickson Types IIa and IIb HLP (isolated hypercholesterolemia and mixed dyslipidemia) using a database pooled across 24 atorvastatin clinical studies. All the studies employed a placebo/diet lead in period and called for monitoring for adherence to a diet low in saturated fat and cholesterol for the duration of the trial. The lipid criterion for inclusion in the pooled analysis was an LDL-C $\geq$ 135 mg/dL, an acceptable definition of hypercholesterolemia (the entry criteria of the original studies excluded patients with marked hypertriglyceridemia; thus for pooling, only an LDL-C criterion is needed). The use of data from the earliest time point and for the first period of a forced titration study is likewise an acceptable analytic approach. Accredited laboratories were used for all the studies and the same formulation of atorvastatin was also used in all the trials. In short, the pooling approach is appropriate and acceptable for the purposes of summarizing the effects of atorvastatin on plasma lipids in patients with Types IIa and IIb HLP.

The response in HDL-C across the dosage range for atorvastatin is consistent with that of the other members of the statin class. It is worth pointing out, however, that there are data from comparative studies that suggest that atorvastatin may not raise HDL-C, on average, to the same degree as simvastatin at doses with comparable LDL-C lowering efficacy. One study, summarized here, was presented at the 48th annual meeting of the American College of Cardiology in early 1999 and subsequently published in the Journal of the American College of Cardiology.

Following a 4-week diet/placebo run-in period, 842 patients with hypercholesterolemia were randomized to one of four treatments: simvastatin 40 or 80 mg or atorvastatin 20 or 40 mg. The active treatment period lasted 12 weeks. Baseline lipids were similar across the randomized groups: LDL-C 213 mg/dL, HDL-C 46 mg/dL, TG 186 mg/dL, and apo A-I 146 mg/dL.

Mean percent changes from baseline in plasma lipids are shown in the table below

	N	LDL-C	TG	HDL-C	Apo A-I	LDL/HDL
Simva 40	202	-43	-23	6.7*	6.3	-46
Atorva 20	210	-45	-23	4.0	5.0	-47
Simva 80	215	-49	-25	6.6*	5.9*	-52
Atorva 40	215	-51	-30	3.0	0.0	-52

* $p < 0.05$ vs. corresponding dose of atorvastatin

While there does appear to be a difference in the effects of these two drugs on HDL-C levels, the impact on clinical effectiveness (cardiovascular disease risk reduction) of these differences is not known. The finding does perhaps send a message of caution in interchanging the two agents in patients at CHD risk. Finally, despite the differences, it is clear that atorvastatin does cause increases in HDL-C in patients with Types IIa and IIb HLP. Modest increases in HDL-C are consistently seen in patients treated with atorvastatin as well as with other statins. As stated in the Introduction, these changes are greater in patients with baseline high TG and thus relatively low HDL-C levels.

In light of the above, though the independent effect of the atorvastatin-associated HDL-C increases on cardiovascular morbidity and mortality are not known, it is appropriate to include mention of the HDL effect in the labeling for the drug, insofar as it is among the panoply of lipid alterations expected with this drug. Consistent with the labeling for other statins and niacins, a disclaimer should also be included in labeling stating that the independent effect of lowering TG or raising HDL-C on CV morbidity and mortality are not known (already in the Lipitor label).

Labeling

Clinical Pharmacology, Clinical Studies, after Table 1, insert:

[redacted]

The sponsor has also requested in a fax dated 11-3-99 addition of the following to the statement above:

[redacted]

This is acceptable with the following changes that render language comparable to the labeling for Zocor (simvastatin):

[redacted]

Indications

The inclusion of the non-HDL-C/HDL-C ratio in the overall indication for the treatment of Types IIa and IIb is not permissible. The list of expected laboratory changes in Indications should be restricted to lipids and lipoproteins alone, and should not include ratios whose pathophysiologic relevance to atherogenesis is not known. The Indications section of the label should read as follows:

[redacted]

[redacted]

The foregoing has been conveyed to the sponsor by telephone on 11-3-99.

Recommendations
Pending agreement on final labeling, this supplement may be approved.

David G. Orloff, M.D.
Medical Team Leader
DMEDP/CDER/FDA

/S/ 11-16-99

Recommendation code: AP

CC:
NDA 20-702 Arch
HFD-510
HFD-510: Shen/Simoneau

I concur
12-2-99
/S/

APPEARS THIS WAY
ON ORIGINAL