CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-702/S025

MEDICAL REVIEW(S)

MEDICAL OFFICER REVIEW

Division of Metabolic and Endocrine Drug Products (HFD-510)

Application #: 20-702/S025 **Application Type:** SE8

Sponsor: Parke-Davis/Pfizer **Proprietary Name:** Lipitor

Investigator: Multiple (Not named) **USAN Name:** atorvastatin

Category: lipid-altering drug **Route of Administration:** oral

Reviewer: Mary H. Parks, MD **Review Date:** May 30, 2001

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission Type	Comments
August 10,2000		SE8	included [redacted] data
October 20, 2000		BL	removed [redacted] data, focused entirely on geriatric labeling

REVIEW SUMMARY:

This supplemental NDA was submitted in accordance with the Geriatric Final Rule 21 *CFR 201.57(f)(10)(iii)* that established a *Geriatric Use* subsection as part of the PRECAUTIONS section of drug labeling. The intention of this final rule was to provide pertinent information about the use of drug products in the elderly (defined as age ≥ 65 yrs) in drug labeling. The data from this submission demonstrate clinically relevant reductions in LDL-C associated with atorvastatin therapy in the geriatric patient population. This benefit was not offset by increases in drug-related adverse events.

The results from this submission will change the following sections of the drug label:

- CLINICAL PHARMACOLOGY; Special Populations subsection
- PRECAUTIONS; Geriatric Use subsection

OUTSTANDING ISSUES: none

RECOMMENDED REGULATORY ACTION:

N drive location:

New clinical studies _____ **Clinical Hold** _____ **Study May Proceed**

NDA, Efficacy/Label supplement: ___X___ **Approval** _____ **Approvable** _____ **Not Approvable**

SIGNATURES:

Medical Reviewer: Mary H. Parks, MD **Date:** May 30, 2001

Medical Team Leader: Mary H. Parks, MD **Date:** May 30, 2001

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ON ORIGINAL

EXECUTIVE SUMMARY

Recommendations on Approvability

Atorvastatin (Lipitor), a member of the statin drug class was approved in 1996 for the treatment of several forms of dyslipidemias. The basis for its approval was the demonstration of clinically relevant reductions in plasma lipoprotein levels, particularly LDL-C. Although LDL-C is a biochemical surrogate measure, the evidence derived from animal models, epidemiologic studies, and familial diseases linking elevated LDL-C levels to CVD risk are overwhelmingly supportive. In recent years, the results of five statin clinical outcome trials have demonstrated reductions in cardiovascular mortality and morbidity associated with LDL-C lowering. In aggregate, these data establish LDL-C as a reliable surrogate measure of risk and the lowering of LDL-C is associated with a clinical benefit.

The benefits associated with LDL-lowering in the large clinical outcome studies are observed across a broad range of baseline cholesterol levels and in both primary and secondary prevention populations. These large placebo-controlled statin trials have also provided information on the risk of chronic therapy for dyslipidemia. These drugs are well tolerated with the primary side-effects of most concern being rare increases in hepatic transaminases and myopathy. In general, such side-effects are readily monitorable and if occur, resolve with interruption or discontinuation of therapy.

Treatment of dyslipidemias with a pharmacologic agent is a chronic, lifelong process as the condition rarely improves with age. If anything, the overall risk of an individual developing heart disease increases over time. As such, the efficacy and safety of these drugs in the elderly patient population need to be evaluated and appropriately conveyed in drug labeling.

This supplemental NDA was submitted in accordance with the Geriatric Final Rule 21 *CFR 201.57(f)(10)(iii)* that established a *Geriatric Use* subsection as part of the PRECAUTIONS section of drug labeling. The intention of this final rule was to provide pertinent information about the use of drug products in the elderly (defined as age ≥ 65 yrs) in drug labeling. The data from this submission demonstrate clinically relevant reductions in LDL-C associated with atorvastatin therapy in the geriatric patient population. This benefit was not offset by increases in drug-related adverse events.

This efficacy supplement should be approved for inclusion of relevant information regarding the efficacy and safety of atorvastatin in the geriatric patient population. The following sections of the Package Insert will be affected:

- CLINICAL PHARMACOLOGY; Special Populations subsection
- PRECAUTIONS; Geriatric Use subsection

Summary of Clinical Findings

Overview of Clinical Program

This application includes efficacy and safety data for atorvastatin 10-80 mg in the geriatric patient population (≥ 65 years) in compliance with the Geriatric Final Rule 21 *CFR 201.57(f)(10)(iii)*. The data are derived from a 54-week open-label, randomized, parallel treatment trial (ACCESS trial) comparing the safety and efficacy of atovastatin to fluvastatin, lovastatin, pravastatin, and simvastatin in patients with primary (Type IIa) or

mixed dyslipidemia (Type IIb). There were 1,958 patients randomized to atorvastatin 10 mg who were subsequently titrated across the approved dosage range (10 to 80 mg) in order to achieve their NCEP LDL-C goal. Additional safety information for atorvastatin was also derived from a 16-week placebo-controlled trial evaluating atorvastatin 80 mg in 3,086 patients with a recent non-Q wave MI or unstable angina (MIRACL trial). Within these two studies, there were 835 elderly patients treated to their NCEP LDL-C goal with atorvastatin 10-80 mg daily and 1,672 elderly patients treated with atorvastatin 80 mg daily for 4 months shortly after experiencing a non-Q wave MI or unstable angina.

Efficacy

The ACCESS trial required patients to have their atorvastatin dose titrated to achieve an LDL-C treatment goal every 6 weeks or until the maximal dose (80 mg) was reached. The efficacy endpoints evaluated in this review included the mean change in LDL-C from baseline at 6 weeks and the proportion of individuals achieving their NCEP LDL-C goal at the end of the study. Results in the elderly subgroup were compared to the non-elderly patients (<65 years) enrolled in this trial.

Baseline characteristics between the two age subgroups were similar with the exception for clinically manifest CVD. The elderly subgroup had a greater proportion of individuals with established cardiovascular or peripheral vascular disease compared to the non-elderly subgroup (78.8% vs. 58.6%).

At 6 weeks the elderly patients achieved a slightly greater mean percent reduction in LDL-C (-38.2%) compared to the non-elderly subgroup (-34.6%). A similar proportion of elderly versus non-elderly patients achieved their NCEP goals. Although there were more elderly patients who required a greater lowering of LDL-C in order to achieve their treatment goal it was interesting that the proportion of elderly subjects requiring titration to the highest dose of atorvastatin was lower in this age group. Approximately 9% of the elderly patients were titrated to atorvastatin 80 mg compared to 12.6% in the non-elderly subgroup. These data suggest a greater degree of LDL-C lowering in the elderly patient population at any dose of drug compared to younger adults.

Safety

The safety of atorvastatin across its dosage range was evaluated in the ACCESS trial with respect to elderly versus non-elderly patients. Since there was no placebo control group in the ACCESS trial it was recognized that certain adverse events observed in the elderly subgroup could not be appropriately compared to the non-elderly subgroup because of confounding factors associated with age. For this reason, additional data on the safety of atorvastatin use in the geriatric population was evaluated in the MIRACL trial, a 16-week placebo control study.

A total of 1,491 (76.1%) of the atorvastatin-treated patients reported an adverse event during the ACCESS trial. Approximately 55% (n=823) of the patients reporting an AE were non-elderly whereas the elderly patients comprised approximately 45% (n=668) of the AEs recorded. The rates of discontinuation due adverse events were similar in the two age groups and there were no differences in clinically relevant laboratory abnormalities between the two subgroups.

The incidence of abnormal liver enzyme elevations was ≤ 1% in both age categories. None of these cases were associated with jaundice or resulted in serious clinical deterioration. No patients experienced rhabdomyolysis during this trial. One patient in each age category reported muscle symptoms associated with CK elevations exceeding 10xULN. Study drug was discontinued in the non-elderly patient who was receiving atorvastatin 20 mg while the elderly patient continued treatment with atorvastatin 10mg. Both patients had normalization of CK values and resolution of symptoms.

More elderly patients reported a serious adverse event compared to non-elderly patients. One hundred forty-nine (13.3%) non-elderly patients experienced a SAE compared to 180 (21.6%) elderly patients. In both groups, the most common SAEs were in the cardiovascular body system including signs and symptoms of coronary artery disease. Since a greater proportion of geriatric patients had more extensive cardiovascular disease at baseline, the higher rate of SAEs due to CV events may have been a reflection of the increased baseline risk. This explanation is supported by the incidence of SAEs reported in the MIRACL trial in which the number of atorvastatin-treated geriatric patients reporting SAEs (11.3%) was similar to placebo-treated geriatric patients (11.4%).

INTRODUCTION

This supplemental NDA was submitted in accordance with the Geriatric Final Rule 21 *CFR 201.57(f)(10)(iii)* that established a *Geriatric Use* subsection as part of the PRECAUTIONS section of drug labeling. The intention of this final rule was to provide pertinent information about the use of drug products in the elderly (defined as age ≥ 65 yrs) in drug labeling.

MATERIALS AND METHODS

Study Design

ACCESS was a 54-week open-label, randomized, parallel treatment trial comparing the safety and efficacy of atovastatin to fluvastatin, lovastatin, pravastatin, and simvastatin in patients with primary (Type IIa) or mixed dyslipidemia (Type IIb). This was a multicenter study involving 158 centers in the United States with 154 centers randomizing patients with or without coronary heart disease (CHD) and/or peripheral vascular disease (PVD).

Study Participants

Of the 7,542 individuals screened for the study, 3,916 were randomized to one of 5 treatment arms: 1,958 to atorvastatin, 497 to fluvastatin, 498 to lovastatin, 481 to pravastatin, and 482 to simvastatin. Within the atorvastatin treatment group there were **835** individuals who were ≥ 65 years of age (elderly subgroup) and **1123** who were < 65 years of age (non-elderly subgroup). The review of this geriatric-labeling supplement will focus only on these 1,958 study participants.

Treatment

Patients in the ACCESS trial had their dose of atorvastatin titrated to reach their NCEP treatment goal. NCEP goals were defined by the individual's risk category as summarized in Table 1. Risk factors included age (> 45 years in men and > 55 years in women), a family history of premature CHD, cigarette smoking, hypertension (HTN), HDL-C < 35 mg/dL, and diabetes mellitus (DM).

Table 1. NCEP LDL-C Treatment Goals

NCEP Risk Category	Target LDL-C Level (NCEP)
No CHD/PVD and 1 or no risk factors	< 160 mg/dL
No CHD/PVD and 2 or more risk factors	< 130 mg/dL
Clinically evident CHD or PVD	≤ 100 mg/dL

All patients were initiated on atorvastatin 10 mg qd therapy. At study weeks 6, 12, and 18, if an individual had not reached his/her NCEP treatment goal the dose of atorvastatin was titrated according to the following schedule.

Table 2. Dose Titration Schedule

Treatment	Start	Wk 6	Wk 12	Wk 18	Wks 24, 30, 42, and 54
atorvastatin	10 mg qd	20 mg qd	40 mg qd	40 mg bid	monitor

Efficacy Parameters

Primary:

The primary efficacy measure was the percent change in LDL-C from baseline at Week 6 and the percentage of patients reaching their NCEP LDL-C goal while on their initial dose at Week 6.

Secondary:

- percent change from baseline in total-C, apoB, HDL-C, LDL/HDL ratio, and TG levels at Week 6 and Week 54
- percent change from baseline in LDL-C to Week 54
- percentage of patients who achieved their NCEP LDL-C goals at Week 54

These parameters were defined based on the ACCESS trial which evaluated the efficacy of atorvastatin compared to 4 other statins. For purposes of this geriatric-labeling supplement, this reviewer is focusing only on the efficacy of atorvastatin within the elderly versus non-elderly population.

Safety Assessments

Two safety parameters were evaluated: the proportion of patient with ALT or AST > 3 x ULN on two consecutive measurements and the proportion of patients with CPK > 10 x ULN on two consecutive measurements associated with muscle pain. ALT and AST levels were obtained at approximately 6 week intervals up to 30 weeks then 12 weeks thereafter. CPK levels were not routinely measured unless muscle symptoms were reported.

Data Analysis

Efficacy analysis was performed on the intent-to-treat (ITT) population defined as all patients randomized who took at least one dose of medication and had valid baseline and post-baseline efficacy measures. Lipid efficacy measures were considered valid if:

- obtained after a minimum 12 hr fast
- post-baseline, the patient had to have taken one dose of medication within 48 hrs of blood draw
- multiple samples were obtained only the first sample, if valid, was used in the analysis

Week 6 efficacy analyses used available data at the week 6 timepoint. Week 54 efficacy analyses allowed for the most recent post-randomization lab values to be carried forward if the Week 54 data were missing.

Safety analyses were performed on all patients randomized who received at least one dose of study medication.

RESULTS OF ACCESS STUDY (limited only to atorvastatin elderly vs non-elderly subgroups)

Baseline Demographics and Patient Characteristics

The baseline characteristics of the atorvastatin treatment group are summarized in Tables 3 and 4 by elderly and non-elderly subgroups. The ratio of males to females was higher in the non-elderly group versus elderly group. Baseline lipid parameters appeared similar between the two subgroups. Not surprisingly, however, the percentage of elderly patients having established cardiovascular or peripheral vascular disease was higher than the non-elderly population (78.8% vs. 58.6%). This observation indicates a greater proportion of elderly patients requiring lipid-lowering treatment to achieve an LDL-C goal < 100 mg/dL.

Table 3. Baseline Characteristics of Atorvastatin Group by Age Categories

	Elderly n=835	Non-Elderly n=1123
Male Female	476 (57%) 359 (43%)	724 (64.5%) 399 (35.5%)
LDL-C, mg/dL mean (SD)	173 (34.4)	181 (38.5)
Total-C, mg/dL mean (SD)	259 (40.9)	267.3 (42.4)
HDL-C, mg/dL mean (SD)	49.1 (12.4)	46.9 (11.7)
TGs, mg/dL mean (SD) median	184.7 (80.7) 168	197.8 (87.7) 183
CHD Risk Group < 2 RF ≥ 2 RF CHD or PVD present	 6.2% 15% **78.8%**	 17.3% 24.1% **58.6%**

derived from ptinfo. xpt and lipid.xpt datasets from ACCESS database

Table 4. Mean Baseline Lipid Values (SD) by CHD Risk Category in Elderly vs. Non-Elderly

	Elderly n=835	Non-Elderly n=1123
< 2 RF	TC 311.5 (43.5) LDL 217.8 (44.4) HDL 58.8 (13.6) TG 174.3 (76.9)	TC 302.6 (44.9) LDL 213.4 (44.7) HDL 52.0 (12.4) TG 191.2 (100.4)
≥ 2 RF	TC 276.3 (39.7) LDL 185.2 (33.4) HDL 51.1 (11.5) TG 201.5 (79.9)	TC 275.1 (35.2) LDL 188.2 (32.6) HDL 46.5 (10.1) TG 202.2 (83.4)
CHD/PVD present	TC 251.6 (36.7) LDL 167.2 (30.2) HDL 47.9 (12.1) TG 182.3 (80.8)	TC 253.5 (36.9) LDL 168.4 (31.8) HDL 45.6 (11.7) TG 197.9 (85.2)

derived from lipid.xpt dataset from ACCESS database

Patient Disposition

Of the 1,958 patients randomized to atorvastatin treatment, 4 never took any medication and 267 (13.6%) did not complete the treatment phase. Table 5 summarizes the reasons for study discontinuation phase by age category.

Table 5. Patient Disposition in Atorvastatin Treatment Group

	Elderly n=835	Non-elderly n=1123
Adverse Events	55 (6.6%)	74 (6.6%)
Other Administrative	47 (5.6%)	91 (8.1%)
withdrew consent	14	17
lost to f/u or moved away	9	39
noncompliance	6	9
MD advice	5	3
trial ended	7	4
other	6	2
Total No. Completing Trial	733 (87.8%)	958 (85.3%)

Source: termol.xpt dataset from ACCESS database

Overall, a similar proportion of elderly and non-elderly participants completed the one-year treatment phase and the incidence of discontinuations due to adverse events was identical between the two age categories. Adverse events will be discussed in detail under the Safety Review section.

Dose Titration

Patients had their atorvastatin dose titrated at visits 6, 12, and 18 in order to achieve their NCEP LDL-C goal. The proportion of individuals requiring treatment with atorvastatin 10, 20, 40, and 80 mg daily was similar between the elderly and non-elderly population (Table 6) although the requirement for 80 mg in the elderly subgroup was slightly lower than the non-elderly group. This observation is interesting given the higher proportion of elderly patients who required treatment to an LDL-C goal of < 100 mg/dL.

Table 6. Atorvastatin Titration to Achieve NCEP Goal by Age Category

Atorvastatin Dose Required	**Elderly n=835**	**Non-elderly n=1123**
10 mg	0.1%	0.4%
20 mg	21%	21%
40 mg	13%	13.7%
80 mg	9%	12.6%

Efficacy Results

Because patients were titrated to an LDL-C goal, a comparison across the entire dosage range of atorvastatin by age subgroups could not be done. For this reason this reviewer evaluated the effects of atorvastatin 10 mg therapy at Week 6 prior to dose titration. The results are summarized in the following table. Lipid data were not available in 70 patients (25 elderly and 45 non-elderly) at Week 6.

Table 7. Changes in LDL-C by Week 6 in Elderly vs. Non-elderly

	Elderly n=810	Non-elderly n=1078
LDL-C at baseline in mg/dL mean (SD)	174.11 (32.1)	181.9 (35.6)
LDL-C achieved in mg/dL mean (SD)	107.1 (24.1)	118.7 (29.7)
Mean % reduction from baseline mean (SD)	-38.2% (10.0)	-34.6% (11.1)

The mean percent reduction in LDL-C from baseline at the 10 mg dose of atorvastatin was greater in the elderly subgroup compared to the younger patients.

Mean percent changes in HDL-C, total-C, and TGs were similar between the elderly versus non-elderly groups (Table 8).

Table 8. Mean Percent Changes in HDL, Total-C, and Triglycerides

	Elderly n=810	Non-elderly n=1078
HDL-C	+6.1% (10.8)	+5.2% (11.2)
Total-C	-27.3% (7.8)	-25.6% (8.7)
TGs	-17.7% (21.8)	-18.1% (24.3)

The greater percent reduction in LDL-C and total-C observed in the elderly patients treated with atorvastatin 10 mg versus the non-elderly patients and the smaller proportion of elderly patients requiring dose titration to 80 mg in order to achieve NCEP goal suggests a greater lipid-lowering response to atorvastatin therapy in the geriatric population.

Safety Results

A total of 1,491 (76.1%) of the atorvastatin-treated patients reported an adverse event during the ACCESS trial. Approximately 55% (n=823) of the patients reporting an AE were non-elderly whereas the elderly patients comprised approximately 45% (n=668) of the AEs recorded.

Deaths and Serious AEs

There were 17 deaths [7 non-elderly (0.06%) and 10 elderly patients (1.2%)] reported. The majority of the deaths were due to cardiovascular causes with the exception for three traumatic causes (1 in nonelderly and 2 in elderly) and esophageal cancer in an elderly patient.

There was a higher incidence of serious AEs reported in the elderly vs. non-elderly patients. One hundred forty-nine (13.3%) non-elderly patients experienced a SAE compared to 180 (21.6%) elderly patients. In both groups, the most common SAEs were in the cardiovascular body system including signs and symptoms of coronary artery disease. Since a greater proportion of geriatric patients had more extensive

cardiovascular disease at baseline, the higher rate of SAEs due to CV events may have been a reflection of baseline risk. Analysis of the safety findings from a 16-week placebo-controlled clinical trial with atorvastatin 80 mg supports this conclusion where a similar number of elderly versus nonelderly patients reported SAEs.

Table 9. Safety Findings in Geriatric Patient Population from a 16-week Placebo-Controlled Trial*

	Placebo	Atorvastatin 80 mg
No. (%) of Patients reporting an SAE	94 (11.4%)	96 (11.3%)
No. (%) of Patients Experiencing a CV Endpoint	190 (26.2%)	184 (26.7%)

*MIRACL database submitted as amendment to Supplement 025

None of the SAEs in the ACCESS or MIRACL trials was due to myopathy/rhabdomyolysis or hepatitis/liver enzyme abnormalities/transaminitis.

Laboratory Abnormalities

Sixteen patients had ALTs > 3xULN, 2 had ASTs > 3xULN, and 14 had both ALTs and ASTs > 3xULN. Table 10 summarizes the elevations in transaminases by age category.

Table 10. Abnormal Liver Enzymes in ACCESS by Age Category

	ALT > 3xULN	AST > 3xULN	ALT/AST > 3xULN
Non-elderly N=1123	n=12 mean 91.4 IU median87.5 IU range 77-135	n=1 96 IU	n=6 mean ALT 136.7 IU range ALT 80-196 mean AST 88.6 range AST 70-110
Elderly N=835	n=4 mean 102.6 IU median 101 IU range 84-127	n=1 78 IU	n=8 mean ALT 210.5 IU range ALT 85-420 mean AST 150.7 range AST 75-286

The incidence of abnormal liver enzyme elevations was ≤ 1% in both age categories. In the patients who had both ALT and AST elevations exceeding 3x the upper limits of normal, the incidence between groups was not appreciably different (0.6% nonelderly vs. 0.9% in elderly). However, the degree of enzyme elevation was slightly higher in the elderly group with both mean ALT and AST values being higher in the elderly subgroup. Only one of these patients had a mildly elevated total bilirubin of 1.2. None of the transaminitis cases resulted in serious clinical sequelae.

Only one patient in each category reported muscle symptoms associated with CK elevations exceeding 10xULN. Study drug was discontinued in the non-elderly patient who was receiving atorvastatin 20 mg while the elderly patient continued treatment with atorvastatin 10mg. Both patients had normalization of CK values and resolution of symptoms.

PROPOSED LABELING

The sponsor proposes the following changes for the Lipitor (atorvastatin) label based on the analysis of the ACCESS trial.

***Geriatric Use* subsection of PRECAUTIONS section**

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To be replaced with:

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MEDICAL OFFICER'S COMMENTS ON REVIEW OF GERIATRIC LABELING SUPPLEMENT

The ACCESS trial was designed to compare the efficacy of several statins across their different dosage ranges to atorvastatin across its dosage range of 10 to 80 mg with respect to reaching NCEP-defined LDL-C goals. The trial was designed as a titrate-to-goal for all treatment arms and evaluated efficacy at 6 weeks and 54 weeks.

The sponsor submitted the results of the ACCESS trial and analyzed the efficacy and safety of atorvastatin treatment by age categories (i.e. < 65 yrs versus ≥ 65 yrs) to fulfill the requirements under 21*CFR 201.57(f)(10)(iii)*, Geriatric Final Rule. A total of 1,958 patients were randomized to received treatment with atorvastatin of which 42.6% (n=835) were elderly and 57.4% (n=1123) were non-elderly.

Because the trial was not a fixed-dose parallel study design, the efficacy and safety between different doses could not be appropriately compared. For this reason, the primary focus of efficacy was on LDL-lowering by Week 6 since this time point evaluated most of the randomized population at the atorvastatin 10 mg dose. At Week 6 the mean percent reduction in LDL-C from baseline was –38.2% in the elderly group compared to –34.6% in the nonelderly group.

Describing efficacy in terms of percentage of patients reaching NCEP goals may be clinically useful; however, this approach can also be misleading if the baseline LDL-C level and cardiac risk factors are not presented. For example, a smaller percent reduction will be needed in those individuals who have a lower baseline LDL-C level and fewer cardiac risk factors than those with higher LDL-C levels and more severe disease.

In this trial, the baseline LDL-C level was similar between the two age groups across the three different cardiac risk categories (see Table 4). However, the proportion of elderly patients with established heart or peripheral vascular disease was 20% higher than the non-elderly group (see Table 3). This would suggest that despite the similar baseline

LDL-C levels in the two age categories the elderly population required a greater mean percent reduction than the non-elderly population in order to achieve their NCEP treatment goal. Interestingly, the proportion of elderly patients requiring the maximum dose of atorvastatin in order to reach NCEP goal was 9% compared to 12.6% in the non-elderly group. Furthermore, mean percent of LDL-lowering achieved with atorvastatin 10 mg was higher in the elderly subgroup than the nonelderly patients. These observations suggest that the elderly population exhibit a higher LDL-lowering response compared to nonelderly patients.

Since this trial lacked a placebo control group the safety findings for atorvastatin-treated patients could not be compared against a background rate of adverse events (i.e. placebo events). Regardless, there were similar percentages of elderly versus nonelderly patients experiencing an adverse event. Although more elderly patients experienced a serious adverse event, primarily cardiovascular, this may be a function of more patients having severe disease in this age group as already discussed. This conclusion is supported by the incidence of SAEs reported in the 16-week placebo-controlled study involving atorvastatin 80 mg daily treatment in patients with a recent coronary event. The rate of SAEs was similar between atorvastatin and placebo in the elderly patient population. Reassuring were the low incidence rates of transaminase elevations and myopathy with none of the few patients who experienced these events having serious clinical consequence.

Despite the study design of ACCESS precluding some conclusions on the efficacy and safety of atorvastatin in the elderly patient population, the results of this one-year study in 835 elderly patients does provide relevant information on the use of this product in the elderly. As such, a description of this trial and its results should be summarized under the *Geriatric Use* subsection of the label.

MEDICAL OFFICER'S COMMENTS ON PROPOSED LABEL

An accurate description of the ACCESS trial including study design and number of elderly versus non-elderly patients randomized to treatment should be included in the *Geriatric Use* subsection. The description of efficacy should not be based on percentage reaching NCEP goal but based on the mean percent change in LDL-C from baseline achieved after 6 weeks of treatment with atorvastatin 10 mg. A statement suggesting a greater responsiveness to atorvastatin in the elderly population may be considered based on a smaller proportion of patients requiring higher doses of atorvastatin in order to achieve targeted LDL-C goals.

This medical reviewer recommends the following changes to the label:

Special Populations

Geriatric: Plasma concentrations of atorvastatin are higher (approximately 40% for Cmax and 30% for AUC) in healthy elderly subjects (age ≥65 years) than in young adults. Clinical data suggest a greater degree of LDL-lowering at any dose of drug in the elderly patient population compared to younger adults (see PRECAUTIONS section: Geriatric Use subsection).

Under PRECAUTIONS section
Geriatric Use

The safety and efficacy of atorvastatin (10-80 mg) in the geriatric population (≥ 65 years of age) was evaluated in the ACCESS study. In this 54-week open-label trial 1,958 patients initiated therapy with atorvastatin 10 mg. Of these, 835 were elderly (≥ 65 years) and 1,123 were non-elderly. The mean change in LDL-C from baseline after 6 weeks of treatment with atorvastatin 10 mg was –38.2% in the elderly patients versus –34.6% in the nonelderly group. The rates of discontinuation due to adverse events were similar between the two age groups. There were no differences in clinically relevant laboratory abnormalities between the age groups.

FINANCIAL DISCLOSURE INFORMATION

No financial disclosure information was submitted, as the ACCESS trial was not considered a covered study for the purposes of supporting geriatric labeling.

RECOMMENDATIONS

Pending labeling negotiations, this application should be approved.

Mary H. Parks, MD
Medical Team Leader
HFD-510

Recommendation code: AP

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