DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

TRANSMITTED VIA FACSIMILE

JUN 2 2 1999

James A. Parker, Jr., Director
Advertising and Labeling
Worldwide Regulatory Affairs
Parke-Davis
201Tabor Road
Morris Plains, NJ 07950

RE: **NDA # 20-702**
Lipitor (atorvastatin calcium) Tablets
MACMIS ID #7784

Dear Mr. Parker:

This letter concerns the dissemination of promotional labeling by Parke-Davis for Lipitor (atorvastatin calcium) tablets. Based on materials[1] that the Division of Drug Marketing, Advertising, and Communications (DDMAC) has received as part of its ongoing monitoring and surveillance program, we have determined that Parke-Davis has disseminated promotional materials for Lipitor that contain false or misleading statements or suggestions in violation of the Federal Food, Drug, and Cosmetic Act. A description of DDMAC's objections is provided below:

1. Unsubstantiated Product Comparison Claims Based on the CURVES Study.

Parke-Davis has disseminated promotional materials which make misleading product comparisons between Lipitor and other statins based on data obtained from the *Comparative Dose Efficacy Study of Atorvastatin Versus Simvastatin, Pravastatin, Lovastatin, and Fluvastatin in Patients with Hypercholesterolemia Study (The CURVES Study).*[2] These claims are unsupported by the CURVES Study, lack substantial

1 These materials include, but are not limited to, the following materials: PD-166-VA-2499-A1 (068) June, 1998, PD-166-SJ-2789-A(088) 809A36 September 1998, and Consumer Brochure PD-166-BK-2550-B1(088)809B88, September 1998.

2 Jones P, Kafonek S, Laurora I, Hunninghake D, for the CURVES investigators. Comparative dose efficacy study of atorvastatin versus simvastatin, pravastatin,

evidence, and are misleading for the following reasons:

- **Misleading Dosage Comparisons between Lipitor and other Statins.** The CURVES Study compared milligram-equivalent doses only (i.e. 10 mg Lipitor to 10 mg pravastatin) for a variety of doses of the four other products. Brochure PD-166-SJ-2789-A1(088) 809A36 (p. 10), however, contains a graph that directly compares Lipitor 10 mg to a variety of doses of simvastatin, lovastatin, and fluvastatin. These graphs and accompanying text are therefore misleading because they compare Lipitor to a variety of dose-ranges of other statins that are unsupported by the CURVES Study.

- **Misleading Dosage Comparisons between Comparator Statins.** The CURVES Study was not designed to support comparisons between statins other than versus Lipitor, only comparisons between milligram-equivalent doses of Lipitor and comparator statins were studied. Several graphs in Brochure PD-166-SJ-2789-A1(088) 809A36, however, invite misleading comparisons of efficacy between comparator statins.

- **Failure to Statistically Account for Multiple Comparisons of Drugs across Doses.** Multiple comparisons of drugs across doses require that statistical corrections[3] be performed in order to provide accurate statistical significance. The graph entitled "LDL-C reductions from baseline at every dose," on p. 14 of Brochure PD-166-SJ-2789-A1(088) 809A36, fails to correct the data it presents to adjust for multiple comparisons across doses. This graph misleadingly suggests that 10 mg of Lipitor can be compared to 20-80 mg doses of the other statins in the CURVES Study. This information, therefore, is false or misleading because the uncorrected comparisons are not statistically valid.

- **Misleading Suggestion that Dosages Were Titrated in the CURVES Study.** The text accompanying the graph on p. 13 of Brochure PD-166-SJ-2789-A1(088) 809A36, states "In a head-to-head trial, the starting dose and usual first titration of LIPITOR provided significantly greater LDL-C reductions." This statement implies that doses of the comparator statins were titrated. The CURVES Study, however, did not titrate doses of Lipitor or other statins. Again on p. 14 of Brochure PD-166-SJ-2789-

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lovastatin, and fluvastatin in patients with hypercholesterolemia (the CURVES Study), *Am J Cardiol.* 1998, 81:582-587.

3 Corrective statistical methods can be applied which allow multiple comparisons to be made within a data set. If these corrective measures are not applied when making multiple comparisons, it is much more likely that a finding may appear to be statistically significant when it is not.

CURVES Study. This impression is further emphasized by the use of asterisked and daggered text stating that LDL-C reductions of other statins across doses, were "significantly less than" Lipitor 10 mg and Lipitor 20 mg doses. In fact, the CURVES Study did not titrate doses of statins nor was it designed to compare non-equivalent doses of statins as indicated by this graph.

- **Failure to Present Confidence Intervals around Point Estimates.** The CURVES Study contained relatively small sample sizes, thereby increasing the likelihood that wide confidence intervals would result from the use of point estimate data. The use of point estimate data alone is misleading without an indication of the variability of the estimates in the CURVES Study due to its small sample size. Specifically, the presentation of the point estimate data contained on p. 14 of Brochure PD-166-SJ-2789-A1(088) 809A36, without indicating the variability of the point estimate results by showing the confidence intervals, is misleading.

- **Unsubstantiated Safety Claims.**

  The front cover of PD-166-VA-2499-A1, describes the CURVES Study and states that "*All statins were well tolerated and no serious adverse events were considered related to any of the study medications.*" Although no serious adverse events may have been observed during the CURVES Study, it would not have been expected that any serious liver enzyme effects would have been be seen, due to the small sample size and short duration of the Study. The safety experience of the CURVES Study is not representative of the experience seen in wider populations with longer-term use of Lipitor. Therefore, such claims are misleading and overstate the safety of this drug. Also, safety claims comparing Lipitor's lack of elevation of liver enzymes with the safety profile of other statins are also misleading for the same reason.[4]

  While it is noted that the back cover of PD-166-VA-2499-A1 does disclose Lipitor risk information related to liver function tests, myopathy, and the contraindication of Lipitor in pregnant or nursing women, this risk information does not provide adequate balance. For example, bolded warning information relative to Lipitor's known association with the development of liver abnormalities, rhabdomyolysis, and acute renal failure are omitted, as is other important risk information related to Lipitor use.

2. Misleading Class Effect Statement

On page 26 of Lipitor Brochure PD-166-SJ-2789-A1(088)809A36, the following statement appears: "Like other statins, LIPITOR inhibits HMG-CoA reductase." A diagram of the mechanism of action follows, and the rest of the page is filled with white space. There is

4 PD 166-SJ-2789-A1(088) 809A36, (p.18): "Well tolerated in clinical trials. In head-to-head clinical trials, LIPITOR provided discontinuation rates comparable with other statins."

no context to include important limiting information with respect to the fact that, although all HMG-CoA reductase inhibitors may share a common cholesterol-lowering mechanism of action, these drug products have not been shown to have the same effects and do not have the same indications. Therefore, it is misleading to suggest that Lipitor has the same effects as the class, by virtue of its mechanism of action.

3. Lack of Fair Balance

The direct-to-consumer Brochure PD-166-BK-255000-B1(088) promotes Lipitor as a method of lowering high cholesterol. The brochure is replete with efficacy information and yet it minimizes the seriousness of important safety information, such as the fact that Lipitor therapy can cause liver toxicity. For example, page 10 of this Brochure states, "People with liver problems should not take Lipitor. Your doctor may do a simple blood test to check your liver." This information does not clearly communicate that these tests are conducted because the use of Lipitor itself might cause liver problems and not just that pre-existing liver problems are a contraindication to the use of Lipitor.

Detailing Brochure PD-166-SJ-2789-A1(088) 809A36 also lacks fair balance. This 28-page brochure is replete with misleading comparative claims, but only discloses risk information on page 18. Moreover, Lipitor's contraindications, and warnings (including bolded warnings, precautions, and adverse events), are presented in small type under a header describing the product as well tolerated. Thus, the content is inadequate and the presentation is clearly not reasonably comparable to the presentation of benefit information in the brochure.

4. Misleading Presentation of Cost Data

Pages 16 and 17 of Brochure PD-166-SJ-2789-A1(088) 809A36, contain claims that Lipitor is "a great value at every dose" and has "lower cost with superior LDL-C reductions." Although nearly half of each page contains blank white space, important cost-limiting information such as "Actual pharmacy costs may differ. Cost comparisons do not imply comparable efficacy or safety," is minimized with tiny footnote-size print. The presentation of cost information without a prominent disclosure regarding important cost limitations, is insufficient to correct the misleading impression that Lipitor's costs to the customer or pharmacy will be lower than competitors at every dose or that its indications are the same as the comparator drugs.

Conclusion and Requested Action

The materials that Parke-Davis has disseminated contain false and/or misleading information about the safety and efficacy of Lipitor. In order to address these objections, DDMAC recommends that Parke-Davis immediately discontinue the promotional use of these pieces and all other materials that contain the same or similar violations.

Parke-Davis should respond in writing to this letter by no later than July 2, 1999. This written response should also include confirmation of Parke-Davis' intent to comply with the above request.

If Parke-Davis has any questions or comments, please contact the undersigned by facsimile at (301) 594-6759, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-40, Rm. 17-B-04, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds you that only written communications are considered official. In all future correspondence regarding this particular matter, please refer to MACMIS ID # 7784, in addition to the NDA number for Lipitor.

Sincerely,

Patricia Kuker Staub, Esq. R.Ph.
Regulatory Counsel
Division of Drug Marketing,
Advertising and Communications