DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

FOI

TRANSMITTED VIA FACSIMILE

Preeti I. Pinto, M.S., M.T. (ASCP)
Quality Assurance Liaison Leader
Astra Pharmaceuticals, L.P.
725 Chesterbrook Blvd.
Wayne, PA 19087-1000

NOV 23 1998

RE: NDA #20-838
Atacand (candesartan cilexetil) Tablets
MACMIS ID #7165

Dear Ms. Pinto:

As part of its routine monitoring program, the Division of Drug Marketing, Advertising and Communications (DDMAC) has become aware of promotional materials for Atacand (candesartan cilexetil) tablets by Astra Pharmaceuticals, L.P. (Astra) that violate the Federal Food, Drug, and Cosmetic Act (Act) and its implementing regulations. Reference is made to selected promotional materials for Atacand, including brochures (157998, 158537, 158538), journal advertisement (158397), clinical highlights brochure (157926), product monograph (158024), magnetic paper clip holder (157631), Dear Doctor letter (157886), and posters (158588, 158589), submitted under cover of Form FDA 2253. DDMAC has reviewed these materials and has determined that they contain promotional claims that are false or misleading, and lacking in fair balance.

Background

DDMAC notes that a number of the violations cited below were previously communicated to Astra in letters from DDMAC, dated June 26, 1998 and August 11, 1998. These letters provided comments on proposed launch promotional materials for Atacand. Further, reference is made to a meeting with the Agency and Astra on August 19, 1998, at which time Astra was informed that its comparative clinical trials of Atacand versus losartan did not provide substantial evidence to support a superiority claim, and therefore would be misleading if presented in promotional materials. Despite guidance from the Agency, Astra has disseminated promotional materials containing these, and numerous other false or misleading claims.

Violations

DDMAC has reviewed the selected promotional materials referenced above and has determined that they are in violation of the Act. Although this letter will provide specific examples of

violations in these materials, DDMAC notes that the same or similar claims or representations are presented in other promotional materials not cited in this letter. DDMAC's comments should be applied to all other promotional materials for Atacand.

Unsubstantiated Superiority Claims

In a brochure (157998) and the product monograph, Astra presents data from a clinical trial, summarized by Andersson et al.,[1] that compared the reduction of sitting diastolic blood pressure (SDBP) in patients receiving once-daily doses of Atacand 8 mg, Atacand 16 mg, losartan 50 mg, or placebo. The graphic representation of the results from this trial depicts that Atacand reduced SDBP to a greater degree than losartan. Further, in the brochure, Astra presents a statistically significant p value (i.e., $p < .05$) for the comparison of the Atacand 16 mg versus losartan 50 mg treatment groups. These presentations clearly imply that Atacand is superior to losartan for the reduction of blood pressure. However, this clinical trial is inadequate in design to support claims of superior efficacy for Atacand over losartan. Claims or representations of superiority over another drug product must be based on substantial evidence derived from adequate and well-controlled clinical trials. Therefore, DDMAC considers any claims of superiority of Atacand over losartan to be misleading because they are not based on substantial evidence. DDMAC notes that Astra presents the disclaimer "[t]hese data are insufficient to demonstrate a claim of superiority" under the graph in the brochure. This disclaimer is inadequate to correct the misleading promotional messages made by presentation of this data.

The Agency's objection to presentation of data from this clinical trial to imply superior efficacy of Atacand over losartan was consistently stated and reiterated in the above cited letters from DDMAC, and in the meeting between the Agency and Astra.

Misrepresentations of efficacy

- In the brochures referenced above, Astra presents the results of a clinical trial, summarized by Franke[2], comparing the efficacy of enalapril 10 mg qd, Atacand 8 mg qd, or placebo. In a graph, Astra presents the mean change in SDBP for Atacand versus enalapril treated patients. Because the resultant decrease in SDBP is not placebo-adjusted, the effects appear greater than those demonstrated in clinical trials evaluating

1. Andersson OK, Neldam S. The antihypertensive effect and tolerability of candesartan cilexetil, a new generation angiotensin II antagonist, in comparison with losartan. *Blood Press*. 1998;7:53-59.

2. Franke H. Antihypertensive effects of candesartan cilexetil, enalapril, and placebo. *J Hum Hypertens*. 1997;11(suppl 2):S61-S62.

Atacand's efficacy. The approved product labeling (PI) describes that trough (24 hour) systolic and diastolic pressures for Atacand compared to placebo, gave effects of about 8-12/4-8 mm Hg with doses of 8-32 mg. Therefore, DDMAC considers this presentation to be misleading because it overstates Atacand's efficacy and is inconsistent with the approved product labeling. Presentations of efficacy measures for Atacand (i.e., changes in blood pressure) should include presentation of the placebo arm, or placebo-adjusted results for the treatment groups.

- In addition, Astra presents the results of a clinical trial, summarized by Farsang et al.[3], comparing the efficacy of amlodipine 5 mg qd, Atacand 16 mg qd, or placebo. In its graphic presentation of results, Astra has failed to present the placebo arm, or to placebo-adjust the efficacy results for the active treatment groups. Thus, for the same reasons cited above, Astra's presentation of the resultant decrease in blood pressure overstates the efficacy of Atacand, and is therefore misleading. DDMAC acknowledges that in our letter, dated August 11, 1998, we stated that we would not object to presentation of this data. However, in the draft materials provided by Astra for DDMAC's review, the presentation of efficacy results appeared to be placebo-adjusted. However, in final form, it is apparent that they are not.

- In the clinical highlights brochure (157926), Astra presents claims adapted from a clinical trial summarized by Reif et al.[4] Again, this graph is misleading because Astra's presentation of the resultant decrease in blood pressure is not placebo-adjusted.

Lacking in fair balance

In general, promotional materials are lacking in fair balance, or otherwise misleading if they fail to present the information relating to the contraindications, warnings, precautions, and side effects associated with the use of a drug in a manner reasonably comparable with the presentation of information relating to the effectiveness of the drug. When presenting risk information, techniques likely to achieve emphasis should be taken into account including, but not limited to typography, layout, contrast, headlines, paragraphing, and white space. Although Atacand therapy is associated with risks, including the boxed warning concerning fetal injury or death if used during pregnancy, Astra's promotional materials repeatedly fail to present risk information associated with

3. Farsang C, Kawecka-Jaszcz K, Langan J, et al. Antihypertensive effects and tolerability of candesartan cilexetil, amlodipine and their combination. *Am J Hypertens*. 1997;10:80A.

4. Reif M, White WB, et al. Effects of candesartan cilexetil in patients with systemic hypertension. *American Journal of Cardiology*. 1998;82:961-965.

the use of Atacand in a manner reasonably comparable to the presentation of efficacy claims, thereby minimizing these risks. The following examples do not comprise a comprehensive list of materials that are lacking in fair balance.

- In its journal advertisement and posters, Astra presents large, colorful, bolded, and bulleted claims for Atacand's efficacy. However, risk information, including information from the boxed warning in Atacand's PI, is confined to the bottom of the materials, in very small sized black type. The risk information is not presented in a manner reasonably comparable to the efficacy claims presented in the journal ad or the poster. This presentation minimizes the importance of the risk information, and is therefore, lacking in fair balance.

- Throughout brochures 158537 and 158538, Astra's presentation of risk information is frequently confined to the bottom of the pages, in small sized type. This is in contrast to the bolded, bulleted claims on these pages of the brochures.

- On the magnetic paper clip holder, Astra presents the claims "Get the power" and "AT_1 receptor site." To balance these claims, Astra makes reference to see the full prescribing information for Atacand, including the boxed warning. DDMAC considers a reference to PI for Atacand to be inadequate to balance these claims, and therefore, this promotional piece is lacking in fair balance.

- All of the risk information in Astra's Dear Doctor letter is presented as footnotes at the bottom of the letter. None of the risk information is presented with the promotional claims contained in the body of the letter.

DDMAC notes that both of our letters to Astra, dated June 26, 1998 and August 11, 1998, stated that we would object to Astra's presentation of risk information in similar draft promotional pieces because Astra frequently presents risk information in small sized type, confined to the bottom of the page, while claims of efficacy are prominently presented in graphs or as bulleted items.

Misrepresentations of mechanism of action

In these promotional materials, Astra presents claims concerning Atacand's mechanism of action and its effect on blood pressure reduction as follows:

- Powerful angiotensin receptor blockade for effective 24-hour BP reduction
- Atacand gets @ the site and stays @ the site
- Atacand exhibits a potent and long-lasting antagonistic effect @ the site
- Atacand exhibits a slow off-rate from the receptor site

- Tight binding @ the AT_1 receptor site
- Long-lasting effect @ the AT_1 receptor site

These claims imply that Atacand possesses clinical advantages due to its receptor binding properties. However, the relationship between receptor binding affinity and clinical effect is unknown. Therefore, presentation of these mechanism of action claims are misleading because they suggest clinical effect, including implying clinical superiority, based on receptor binding properties, when no such clinical relevance has been demonstrated by substantial evidence. .

DDMAC notes that in our June 26 and August 11, 1998 letters, DDMAC stated that we would object to comparative claims or implications based on receptor binding properties, and to combining claims based on mechanism of action with clinical efficacy claims because the clinical relevance is unknown.

Misrepresentations of dosing and administration

In the brochures, Astra presents the following, or similar, claims concerning the dosing and administration of Atacand:

- 24-hour BP reduction with once-daily dosing
- The usual starting dose for Atacand is 16 mg once daily, with 8 mg and 32 mg also available for individualization of therapy

These claims imply that Atacand can only be administered once daily. However, the Dosing and Administration section of the PI for Atacand states the following:

Dosage must be individualized. Blood pressure response is dose related over the range of 2-32 mg. The usual recommended starting dose of Atacand is 16 mg once daily when it is used as monotherapy in patients who are not volume depleted. Atacand can be administered once or twice daily with total daily doses ranging from 8 mg to 32 mg.

With the exception of the product monograph, Astra fails to provide information concerning the twice daily dosing regimen in any of the promotional pieces that describe dosing and administration information of Atacand. Therefore, DDMAC considers these claims to be misleading and inconsistent with the PI because they lack context for the recommended dosing and administration of Atacand. DDMAC notes that these same comments were provided to Astra in our letters, dated June 26, 1998 and August 11, 1998.

Astra should immediately cease distribution of these promotional materials, and all other promotional materials for Atacand that contain the same or similar claims or presentations. Astra should submit a written response to DDMAC, on or before December 9, 1998, describing its intent and plans to comply with the above. In its letter to DDMAC, Astra should include a list of all promotional materials that were discontinued, and the discontinuation date.

Astra should direct its response to the undersigned by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-40, Rm 17B-20, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds Astra that only written communications are considered official.

In all correspondence regarding this particular submission, please refer to MACMIS ID #7165 in addition to the NDA number.

Sincerely,

Janet M. Norden, MSN, RN
Regulatory Review Officer
Division of Drug Marketing,
Advertising and Communications