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DEPARTMENT OF HEALTH & HUMAN SERVICES
Food and Drug Administration
New England District

Food and Drug Administration
One Montvale Avenue
Stoneham, Massachusetts 02180
(781)279-1675 FAX: (781)279-1742

WARNING LETTER

September 14, 1998
(Corrected November 19, 1998)

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

NWE-21-98W

Ivan Rowley, President and CEO
Astra USA
50 Otis Street
Westborough, Massachusetts 01581

Dear Mr. Rowley:

During an inspection of your manufacturing facility in Westborough, Massachusetts conducted on June 10, 11, 12, 15, and 17, 1998, our Investigator determined that your firm is currently marketing 4% Citanest Forte with Epinephrine without an approved NDA supplement. At the conclusion of the inspection, a Form FDA 483, Inspectional Observations, was presented to Dennis J. Bucceri, V.P. Regulatory Affairs. A copy of the FDA 483 is enclosed for your information.

The inspection found that 4% Citanest Forte with Epinephrine, as currently manufactured, is a new drug for which no supplemental new drug application (NDA) has been approved and, as such, violates Section 505(a) of the FD&C Act in that product has been introduced or delivered for introduction into interstate commerce without such approval.

In 1990 the United States Pharmacopeia 21 (USP XXI), eighth supplement broadened the limits for the epinephrine content from equivalent to not less than 90 percent and not more than 110 percent of the labeled amount, to equivalent to not less than 90 percent and not more than 115 percent of the labeled amount of epinephrine. On July 5, 1990, Astra filed a NDA Special Supplement - Change in Effect for Citanest with epinephrine solution that requested: 1) [REDACTED]

Your firm then increased the

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amount of epinephrine from 108 percent to 111 percent. The agency was notified of this processing change through an annual report dated November 9, 1990, which indicated an increase in epinephrine. We find that this change constitutes a change in the method of manufacturing and requires that a supplement to the NDA be submitted and approved prior to any commercial distribution as directed under 21 CFR 314.70(b)(2)(i).

We are in receipt of a letter dated June 22, 1998, from Joseph J. Anisko that responds to the observations listed in the FDA 483, and it is currently under review. We note that as of June 28, 1998, your firm is no longer manufacturing 4% Ciganest Forte with Epinephrine and will not resume manufacturing the product until one of the following occurs:

1. The 111% overage issue is resolved with the Center, or
2. Astra runs out of its existing supply, projected to be August 1998. Astra will then commence producing product in accordance with the approved NDA at 108% overage with an expiry of fifteen (15) months..

On July 29, 1998, Bruce R. Ota spoke to David Pizzi and Russell Doughty. Mr. Ota informed both Mr. Doughty and Mr. Pizzi that the Center for Drugs Evaluation and Research (CDER) said the fifteen (15) month expiry time was unacceptable and that documentation would only support a twelve (12) month expiry time. Mr. Ota also told them they should either call Ken Nolan or Pramodu Matura from CDER to discuss this issue. We understand a dialogue is ongoing.

The above is not intended to be an all-inclusive list of violations which may exist at your firm. As top management, it is your responsibility to ensure that all requirements of the cGMP regulations are being met as well as all other requirements of the Act.

Federal agencies are advised of the issuance of all Warning Letters about drugs and devices so that they may take this information into account when considering the award of contracts.

Please advise this office in writing within fifteen (15) days of receipt of this letter as to any additional specific actions you have taken or intend to take to correct the violation. Your reply should be directed to the attention of Bruce R. Ota, Compliance Officer at the above address.

Sincerely,

John R. Marzilli
District Director
New England District Office