DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

TRANSMITTED VIA FACSIMILE

NOV 24 1998

Robert C. Black
President
Zeneca Pharmaceuticals
1800 Concord Pike
Wilmington, DE 19850

RE: NDA No. 19-777 Zestril (lisinopril) tablets
NDA No. 20-356 Sular (nisoldipine) tablets
NDA No. 17-970 Nolvadex (tamoxifen citrate) tablets
NDA No. 20-768 Zomig (zolmitriptan) tablets
NDA No. 20-498 Casodex (bicalutamide) tablets
MACMIS ID # 7113

WARNING LETTER

Dear Mr. Black:

This Warning Letter concerns Zeneca Pharmaceuticals' (Zeneca) dissemination of promotional materials for its products Zestril (lisinopril), Sular (nisoldipine), Nolvadex (tamoxifen citrate), Zomig (zolmitriptan), and Casodex (bicalutamide). The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed these materials as part of its monitoring and surveillance program. DDMAC has concluded that the Zeneca promotional materials cited in this letter are false or misleading and lacking in fair balance in violation of the Federal Food, Drug, and Cosmetic Act (Act), 21 USC § 331(a), (b), (d), 352(a), (n), 355(a), and applicable regulations. Specifically, these materials fail to prominently or adequately convey the risks or other information associated with the use of these drugs. Further, promotional materials for Zomig and Casodex contain unsubstantiated safety or efficacy claims that raise significant patient safety concerns. By its dissemination of these misleading promotional materials, Zeneca is misbranding Zestril, Sular, Nolvadex, Zomig, and Casodex.

Prominence and readability

Promotional materials are false or misleading, lacking in fair balance, or otherwise misleading if they fail to present the information relating to contraindications, warnings, precautions, and side effects associated with the use of a drug with a prominence and readability reasonably comparable to the presentation of information relating to the effectiveness of the drug. In addition, promotional materials are false or misleading if they do not present necessary

contextual information with reasonably comparable prominence to the presentation of the claim. In reviewing the presentation of such information, techniques likely to achieve emphasis are taken into account including, but not limited to typography, layout, contrast, headlines, paragraphing, and white space. DDMAC concludes from its review of promotional materials for Zestril, Sular, Nolvadex, and Zomig, that Zeneca failed to present risk and/or contextual information in a reasonably comparable manner, as follows:

Risk information

- Zeneca disseminated a journal advertisement for Zestril identified as ZS1247, published in *The Physician Assistants' Prescribing Reference,* Fall 1998. In this advertisement, Zeneca prominently presents several claims concerning the efficacy of Zestril. However, what appears to be the risk information associated with the use of Zestril, is confined to the bottom corner of the advertisement. Furthermore, the extremely small type size and lack of contrast with the background render the risk information illegible.

- Zeneca submitted, under cover of Form FDA 2253, a journal advertisement for Sular identified as SL1142. Claims for the efficacy of Sular are presented in bolded, bulleted type. In contrast, the statements concerning adverse effects and limitations of Sular therapy are presented in small sized type beneath these claims.

- Zeneca submitted, under cover of Form FDA 2253, two journal advertisements for Nolvadex identified as NL1134 and NL1149. Both of these advertisements contain prominent claims for the safety of Nolvadex, such as "well tolerated" and "well-documented safety profile" in the text of the advertisements. However, risk information is presented as a footnote.

- Zeneca submitted, under cover of Form FDA 2253, a journal advertisement for Zomig identified as ZM1058. In this advertisement, the risk information is presented in a tiny thin-lined font, as a footnote at the bottom of the page.

Contextual information to qualify efficacy claims

- In the journal advertisement identified as NL1149, Zeneca prominently presented the claim that "...Nolvadex significantly prolongs overall survival by 17%, regardless of nodal or menopausal status." This claims misleadingly suggests that Nolvadex is indicated for use in the adjuvant setting, regardless of nodal or menopausal status. However, Nolvadex is not indicated for premenopausal node-positive patients in the adjuvant setting. To present this important limitation, Zeneca used a small type-size footnote (i.e., "Nolvadex is not indicated for premenopausal node-positive patients"). This footnote is separated from the claim it qualifies and lacks prominence necessary to qualify the limitations of the indications for use.

- Zeneca submitted, under cover of Form FDA 2253, a promotional leaflet for Zomig, identified as MN1480. In this leaflet, Zeneca misleadingly presented claims concerning Zomig's mechanism of action. However, the mechanism of action for Zomig has not been established. Although Zeneca presented a footnote, in very small sized type, that "the etiology and pathophysiology of migraine remains theoretical...," this disclosure is not sufficiently prominent to qualify the mechanism of action claims.

Disclosure of risk information

Promotional materials are false, lacking in fair balance or otherwise misleading if they contain a representation or suggestion, that a drug is safer, has less incidence of, or less serious side effects or contraindications than has been demonstrated by substantial evidence or substantial clinical experience. DDMAC concludes from its review of promotional materials for Zestril, Sular, Zomig, and Casodex that Zeneca failed to adequately disclose important risk information associated with the use of these drugs, as follows:

- In the journal advertisement for Zestril described above, DDMAC cannot determine whether the content of the risk information is adequate because the risk information is illegible.

- In the journal advertisement for Sular referenced above, Zeneca presented that "[t]he most common side effects with SULAR are headache and peripheral edema. The safety of SULAR in patients with heart failure has not been established." However, Sular is associated with other adverse reactions related to its vasodilatory properties, such as dizziness. In addition, the use of Sular in certain patient populations requires close observation and dose adjustments. Some of these risks are associated with the effects of the drug, some with the patient's clinical status, and some with interactions between Sular and concomitant drug therapies. Zeneca's current presentation of risk information is inadequate to accurately disclose the risks associated with the use of Sular.

- In the leaflet for Zomig referenced above, Zeneca claimed that Zomig is safe and well-tolerated, and characterized the adverse events associated with Zomig as "typically mild and transient and did not lead to long-lasting effects." However, Zeneca failed to present the warning concerning the risk of coronary artery vasospasm or any information concerning the most common adverse events associated with Zomig's use.

  Furthermore, in this leaflet, Zeneca presented claims that Zomig has been used safely with fluoxetine, acetaminophen, propranolol, and metoclopamide. However, Zeneca failed to disclose information concerning the drug-drug interactions with these, and other drugs, with Zomig. For example, fluoxetine, and other selective serotonin reuptake inhibitors have been reported to cause weakness, hyperreflexia, and incoordination when coadministered with $5HT_1$ agonists; Zomig delayed the T_{max} of acetaminophen by one hour; and propranolol

affects the pharmacokinetics of Zomig and its active metabolite. In addition, due to significant drug-drug interactions (i.e., potential vasospastic reactions), use of ergotamine-containing or ergot-type medications and Zomig within 24 hours of each other should be avoided. Furthermore, monoamine oxidase A (MAO A) inhibitors increase the systemic exposure of Zomig, so coadministration of MAO A inhibitors or use of Zomig within two weeks of discontinuation of MAO A inhibitor therapy is contraindicated. Selectively presenting information concerning drugs that have been safely used with Zomig, without disclosure of the potential consequences of coadministration with these, and other drugs, could lead to potential drug-drug interactions and unnecessary risk to patients.

- At the promotional exhibit area at the annual meeting of the American Urological Association, San Diego, California, on June 1 and 2, 1998, Zeneca disseminated three promotional labeling pieces, consisting of one-page leaflets that present excerpts from clinical trials[1,2,3]. Although all three leaflets contain claims that Casodex was safe and well tolerated, two of the leaflets present no information about the risks and adverse events associated with the use of Casodex therapy. In the leaflet identified in footnote #2, Zeneca stated that "[t]he overall incidence of adverse events was comparable between the treatment arms, with the exception of the expected pharmacologic side effects for the 2 treatments (i.e., gynecomastia and breast pain for CASODEX, and hot flushes for castration)." However, Zeneca failed to present information related to other risks associated with Casodex therapy, including appropriate reference to the precautions and contraindications.

Unsubstantiated Safety and Efficacy Claims

Promotional materials are false, lacking in fair balance or otherwise misleading if they contain a representation or suggestion, not approved in the labeling, that a drug is more effective, safer, or useful in a broader range of conditions or patients than has been demonstrated by substantial evidence or substantial clinical experience. Furthermore, promotional materials are false or misleading if they use literature, quotations, or references for the purpose of recommending or suggesting conditions of drug use that are not approved or permitted in the drug package labeling or use data favorable to a drug derived from patients treated with dosages different from those recommended in approved or permitted labeling. DDMAC concludes from its review of the above referenced promotional materials for Zomig and Casodex that they contain unsubstantiated

---

1. "Bicalutamide (B) Monotherapy Versus Flutamide (F) plus Goserelin (G) in Prostate Cancer (CA) Patients (Pts). Preliminary Results of an Italian Prostate Cancer (PONCAP) Study."

2. "CASODEX (bicalutamide) 150 mg Monotherapy - Survival Outcome Comparable to Castration with Quality of Life Advantages."

3. "Ongoing Trials Compare CASODEX (bicalutamide) 150 mg Monotherapy vs Placebo in Early Prostate Cancer Patients."

efficacy claims. Further, the promotional materials for Casodex also contain unsubstantiated safety claims, and recommendations for use in conditions or dosages that are inconsistent with the approved product labeling.

Zomig

In the promotional materials referenced above, Zeneca presented the claim that Zomig has the "power to turn off migraine." This claim implies that Zomig is an abortive treatment for migraine. Although Zomig has demonstrated the ability to relieve migraine pain in some patients at two hours, it has not been shown to abort the migraine attack itself, including alleviating all the other migraine-associated symptoms. Therefore, this claim is misleading because it implies that Zomig has broader efficacy than has been demonstrated by substantial evidence.

Casodex

The approved product labeling for Casodex states that it is indicated for use in combination therapy with a lutenizing hormone-releasing hormone (LHRH) analogue for the treatment of Stage D_2 metastatic carcinoma of the prostate. The approved product labeling also states that the recommended dosage for Casodex therapy in combination with LHRH analogue is 50 mg per day, and that treatment with Casodex should be started at the same time as treatment with an LHRH analogue.

The promotional leaflets referenced above for Casodex are in violation of the Act because they state or suggest that Casodex is safe and effective:

- in patients with early, non-metastatic (T1b/T1c/T2/T3/T4), or locally advanced prostate cancer;
- when used as monotherapy (without LHRH analogue); and
- at doses of 150 mg per day (three times higher than the dose recommended in the approved product labeling).

Zeneca's dissemination of promotional materials that state or suggest that Casodex is safe and effective as monotherapy for patients with earlier stages of the disease, and at three times the recommended dose, in combination with inadequate presentation of risk information, raises significant public health and safety concerns.

Conclusions and Requested Actions

Zeneca has disseminated promotional materials that contain false or misleading information, or are lacking in fair balance for Zestril, Sular, Nolvadex, Zomig, and Casodex. Accordingly, Zeneca should propose an action plan that includes:

1. immediately ceasing the dissemination of these materials and all other advertising and promotional labeling materials for these products that contain false or misleading claims, or fail to clearly, adequately, and prominently disclose risk or contextual information in a manner reasonably comparable to the benefit claims;

2. reviewing its promotional materials for all of its products and to discontinue or revise any materials with the same or similar violations;

3. providing a complete listing of all materials for all of its products that will remain in use and those that will be discontinued;

4. submitting a written statement of Zeneca's intent to comply with "1," "2," and "3" above; and

5. submitting a proposal to disseminate accurate and complete information to the audiences that received Zeneca's misleading messages.

The violations discussed in this letter do not necessarily constitute an exhaustive list. We are continuing to evaluate other aspects of Zeneca's promotion of these products and may determine that there are additional violations and that additional remedial measures will be necessary to fully correct the misleading messages resulting from Zeneca's violative conduct.

Zeneca's response should be received no later that December 10, 1998. If Zeneca has any questions or comments, please contact Janet Norden, RN, MSN, Lesley Frank, Ph.D, J.D., or Norman Drezin, R.Ph., J.D. 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, Maryland 20857. DDMAC reminds Zeneca that only written communications are considered official.

In all correspondence regarding this particular matter, please refer to MACMIS ID #7113 in addition to the NDA numbers.

Failure to respond to this letter may result in regulatory action, including seizure or injunction, without further notice.

Sincerely,

Minnie Baylor-Henry

Minnie Baylor-Henry, R.Ph., J.D.
Director
Division of Drug Marketing,
Advertising and Communications