DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

MAR 15 2000

TRANSMITTED VIA FACSIMILE

Michele M. Hardy
Director, Advertising and Labeling Policy
Regulatory Affairs
Glaxo Wellcome Inc.
Five Moore Drive
P.O. Box 13398
Research Triangle Park
North Carolina 27709

RE: NDA 21-036
Relenza (zanamivir for inhalation)
MACMIS ID#8708

Dear Ms. Hardy:

This letter concerns Glaxo Wellcome Inc.'s (GW) promotional materials for Relenza. The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed these promotional materials as part of its routine monitoring and surveillance program. From its review, DDMAC has concluded that GW has distributed materials that are false and/or misleading, in violation of the Federal Food, Drug, and Cosmetic Act and its implementing regulations.

In promotional materials,[1] you have presented product information that lacks fair balance, contains misleading safety and efficacy claims, unsubstantiated comparative claims, misleading drug resistance claims, and misleading productivity and pharmacoeconomic claims.

Lacking in Fair Balance

In general, information relating to risk information should be presented in a manner reasonably comparable to the overall presentation of information relating to the effectiveness of the drug. In your brochure, RLZ046RO, you have prominently presented multiple efficacy claims in at least 12 pages, with bar graphs, illustrations, and white space. In contrast, only one page of risk information is presented and this presentation fails to include important safety information from the Precaution section of the approved labeling. Also, the bolded precaution is not presented with sufficient prominence. GW fails to include the following precautions:

[1] RLZ046RO (brochure), RLZ060RO (journal ad), RLZ104RO (electronic slide kit), RLZ071 (patient brochure), RLZ048RO (slide kit), RLZ100RO (formulary kit), RLZ096RO (card)--not all inclusive--

- This product [Relenza] has not been shown to be effective, and may carry a risk, in patients with severe or decompensated chronic obstructive pulmonary disease or asthma. Any patient who develops bronchospasm or decline in lung function should stop the drug and contact their physician promptly if they experience worsening respiratory symptoms.

- Patients with underlying disease should be instructed to have a fast-acting inhaled bronchodilator available. Patients scheduled to use an inhaled bronchodilator at the same time as Relenza should use their bronchodilator before taking Relenza.

Unsubstantiated Claims

In your journal ad, RLZ060RO, and slide kit, RLZ104RO, you misleadingly present graphic illustrations of an inhaler with arrows pointing directly into the lungs and a two-dimensional scintigraphic imaging scan of the lungs, respectively. These illustrations are presented in conjunction with statements, ***"Reach the lungs and help move influenza out," "New, inhaled Relenza delivers antiviral action to the lungs and shortens the course of the flu," "Delivers antiviral action to the primary site of viral replication," and "Local application with low systemic exposure,"*** that are misleading because they suggest that most of Relenza has been proven to enter the lungs and Relenza has demonstrated topical antiviral activity at the site when such has not been demonstrated by substantial evidence. In fact, distribution studies, including the article in Clinical Pharmacokinetics by Cass, L., Brown, J., Pickford, M., et al (1999), that you have submitted, do not support the suggestion that Relenza is mostly distributed into the lungs, even with the most optimistic interpretation of the data. On the contrary, the supporting documents proposed that most of Relenza is delivered to the oropharynx. Further, you have not performed studies to adequately support the suggested claim of topical activity in the lungs for Relenza.

Misleading Comparative Claim

You have misleadingly presented unsupported implied comparative claims in the promotional piece, RLZ071RO. In this piece, the statements, ***"Unlike over-the-counter medicines that treat flu symptoms, inhaled prescription Relenza works on the virus itself" and "A timely advance in flu treatment,"*** are misleading because they are implied comparative statements that suggest that Relenza is more effective or more advanced than over-the-counter medicines or other flu treatments when such has not been demonstrated by substantial evidence. Further, you misleadingly imply that Relenza is more effective because of its *in vitro* antiviral activity, when the product labeling states that the relationship between the *in vitro* inhibition of influenza virus by zanamivir and the inhibition of influenza virus replication in humans has not been established.

Overstatement of Efficacy

The promotional piece, RLZ046RO, is misleading because it suggests that Relenza has demonstrated efficacy for all of the *individual* flu symptoms listed—fever, cough, myalgia/arthralgia, sore throat, and headache, when such has not been demonstrated by substantial evidence. In addition, symptom relief by up to one day was not demonstrated for all patients and symptom relief may not be sustained since the pivotal trials showed

some fluctuation of symptoms after the primary study endpoint was reached in both treatment groups.

In addition, your presentation of efficacy in RLZ046RO is misleading because you have omitted appropriate qualification or pertinent information from the approved product labeling to understand the efficacy limitations of Relenza. Specifically, you have presented multiple efficacy claims but have omitted the following information:

- No consistent treatment effect was demonstrated in patients with underlying chronic medical conditions, including respiratory or cardiovascular disease.
- No consistent differences in rate of development of complications were observed between treatment groups.
- Some fluctuation of symptoms was observed after the primary study endpoint in both treatment groups.
- No information is available regarding treatment of influenza in patients with any medical condition sufficiently severe or unstable to be considered at imminent risk of requiring inpatient management.

Misleading Efficacy Statement
In the promotional piece, RLZ046RO, the statement, ***"Patients judged to be in population groups most likely to benefit include: Patients with higher baseline temperatures (38.2°C/100°F [sic] or more) and patients judged to have more severe symptoms,"*** is misleading because it is inconsistent with the approved product labeling. The approved labeling states that patients with a lower temperature (e.g. 38.2°C or less) or investigator-rated as having less severe symptoms derived less benefit from Relenza.

Misleading Drug Resistance Claims
In your slide kit, RLZ048RO, and brochure, RLZ046RO, the statement, ***"No treatment-emergent resistance in clinical trials,"*** is misleading because it suggests that lack of resistance in zanamivir-treated patients has been established by substantial evidence. Many of the clinical trials specimens were assayed only for neuraminidase enzyme activity which was not an acceptable form of documentation for detecting the lack of resistance, because the measurement of a single enzyme does not give full information about the ability of the virus to persist in the presence of the drug. In fact, the approved product labeling states that insufficient information is available to characterize the risk of emergence of zanamivir resistance in clinical use.

Further, the statement, ***"One case of resistance was reported in an immunocompromised pediatric patient. This pediatric patient received ribavirin for 2 weeks prior to being given an investigational nebulized solution of Relenza in an emergency, compassionate-use situation,"*** is misleading because it implies that resistance occurred prior to zanamivir treatment and suggests that resistance occurred during ribavirin treatment. However, according to the product labeling, resistance emerged after the patient was treated with zanamivir.

Misleading Productivity and Pharmocoeconomic Claims

In promotional materials, RLZ071RO and RLZ046RO, you misleadingly suggest that Relenza has demonstrated an impact on patient productivity. Specifically, you present misleading graphic illustrations of Relenza's impact on productivity by presenting patients before (ill in bed) and after (back to work or play) the flu in conjunction with misleading statements, ***"New inhaled Relenza—Even a day can make a difference," "She could miss the busiest day of the year," "He could miss the playoff game," "She could miss the school bake sale," "He could miss the annual stockholders meeting," "She could miss her granddaughter's recital," and "So when the flu virus gets you, you can get it back, and get back to your life—sooner."*** These presentations and statements are misleading because they imply that Relenza improves functional status, which is unsubstantiated.

Further, the formulary kit, RLZ100RO, and promotional card, RLZ096RO, are misleading because you present the economic burden of influenza and misleadingly suggest that Relenza positively impacts medical costs and productivity loss, when such has not been demonstrated by adequate evidence. While your referenced studies evaluate the costs of influenza to society, they do not demonstrate that the "suggested up to one day" reduction of symptoms with Relenza has an impact on costs.

In addition, the presentation of the statement in promotional materials for Relenza, ***"Influenza afflicts 25 to 55 million people annually in the United States, resulting in 20,000 deaths and 50,000 to 300,000 hospitalizations,"*** would be misleading because this presentation suggests that Relenza has been shown to impact hospitalizations and deaths from influenza when such has not been demonstrated by substantial evidence. Further, you have not disclosed that risks for hospitalization and death from influenza are higher among persons aged greater than or equal to 65 years and persons of any age with underlying high-risk medical conditions; populations for which efficacy of Relenza has not been demonstrated by substantial evidence.

Requested Actions

GW should immediately cease publication or dissemination of promotional materials or activities that contain these or similar claims. In addition, GW should respond in writing no later March 27, 2000, describing its plan to comply. GW should also include a list of all similarly violative materials being discontinued, as well as the date of discontinuation.

We acknowledge that you have discontinued promotional piece, RLZ071RO, because it contained claims that suggests that Relenza is more effective than has been demonstrated by substantial evidence. However, similar misleading comparative claims referenced in this piece and contained in other materials should also be discontinued.

Your response should be directed to Ele Ibarra-Pratt by fax at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-42, 17B-20, 5600 Fishers Lane, Rockville, MD 20857. We remind you that only written communications are considered official.

In all future correspondence regarding this particular matter, please refer to MACMIS ID #8708 in addition to the NDA number.

Sincerely,

/S/

~~Eli~~ Ibarra-Pratt, R.N., M.P.H.
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications