Division Director Memorandum

NDA:	**21-036**
Drug and indication:	**Relenza® (zanamivir for inhalation) for treatment of influenza**
Dose:	**10 mg (2 inhalations) b.i.d. for 5 days**
Applicant:	**Glaxo Wellcome Inc.**
Submission dated:	**October 26, 1998**
Date of Memorandum:	**July 26, 1999**

In this application, the sponsor has requested approval for zanamivir inhaled dry powder for the treatment of uncomplicated influenza in adults and adolescents 12 years and older who have been symptomatic for no more than two days. In support of this request, the sponsor has submitted results of three placebo-controlled phase III clinical trials conducted in North America, Europe and the Southern Hemisphere. These trials enrolled 1588 patients, of whom 1164 were diagnosed influenza-positive with either influenza A (89%) or influenza B (11%). Additional support for the activity of this agent has been provided by the results of phase II trials, influenza challenge studies and a community prophylaxis study.

This application was discussed at a meeting of the Antiviral Drug Products Advisory Committee on February 24, 1999. The primary issues raised included: discordance between results of the North American study and the two non-U.S. trials; the uncertain relevance of foreign data for a U.S. regulatory action; the need for additional analyses regarding symptom occurrence after initial alleviation; questions about whether the treatment effect represented a clinically meaningful impact on illness duration; safety in patients with underlying respiratory disease; the uncertain potential for emergence of viral resistance; and whether patients could adequately master use of the device during short-term treatment. On the basis of these issues, the majority of the participants voted against approval of this application at that time.

In follow-up to this meeting, a detailed information request letter (dated March 17, 1999) was issued to the sponsor. The purpose of this letter was to provide an opportunity for the sponsor to address concerns raised by the Advisory Committee through submission of additional data and analyses. The sponsor's response included further investigation of the following: treatment response in relevant subgroups; alternative approaches to address potential minimization (confounding) of treatment effect by relief medication; symptom occurrence after initial alleviation; safety in patients with underlying pulmonary disease and others; and the effect of zanamivir in influenza-negative subjects. Subsequently, proposals to address other outstanding issues during phase IV have been submitted.

With the additional analyses provided, I believe that issues raised at the Advisory Committee

meeting have either been resolved, or have been adequately addressed in product labeling and/or in phase IV commitments. Therefore, I am in concurrence with the consensus of the clinical reviewers that this product confers a modest clinical benefit in patients with uncomplicated influenza and that this benefit is appropriately balanced by the product's tolerability profile. I additionally share the clinical team's perspective that current influenza treatment options are limited, that there is no approved product with activity against influenza B virus, and that this product will offer an alternative therapeutic approach for an important public health problem. Accordingly, I support their recommendation that this application be approved.

As evidenced by the nature of issues raised by the Advisory Committee members and in the clinical and biometrics reviews, this complex clinical database needs to be interpreted within a perspective that takes into account the course of uncomplicated influenza and the inherent challenges in conducting clinical trials for this acute, self-limited indication. In this memorandum, I would like to discuss my perspective on this database and my rationale for recommending approval for treatment of uncomplicated influenza. Additionally, I would like to comment on other noteworthy aspects of this application.

1. Relevant background

Throughout the clinical development of this product, numerous discussions have occurred between the sponsor and the Division regarding the unique challenges of demonstrating efficacy in the treatment of uncomplicated influenza. Based on review of prior applications for amantadine and rimantadine and the sponsor's phase II zanamivir data, the Division discussed with the sponsor that it may be difficult to show a convincing treatment effect in an otherwise healthy patient population with an acute, self-limited illness. Recognized challenges for clinical trial design for this indication include: the acute, brief and self-limited nature of the illness; the subjectivity of any endpoint that attempts to capture the intensity of symptoms; the limited expectation for the role of an antiviral agent once infection with influenza is established; minimization of any treatment effect by use of symptomatic relief medications; and the necessary reliance on self-reported data.

The Division's approach to the review of the rimantadine database in the 1980's reflected an appreciation of the constraints in antiviral drug development for this indication. Rimantadine's approval for the treatment indication was based on the results of smaller, narrowly focused studies in which a total of 126 evaluable patients received rimantadine. In the Division Director's memorandum that recommended approval (dated November 2, 1988), it is clear that although the data in support of approval for treatment were not strong, the practical difficulties of performing studies in this illness were felt to be appreciable, and the more robust data for the prophylaxis indication were considered supportive of both safety and antiviral activity.

Although the zanamivir application contains larger, more uniformly conducted studies and more prospectively defined analyses than those submitted in support of either rimantadine's or amantadine's efficacy for treatment, this application has raised several similar review issues in trying to integrate trials with variable results.

2. Integration of principal efficacy results and additional supportive information
Please refer to Dr. Barbara Styrt's Medical Officer review for a comprehensive discussion of the clinical database. I am in overall agreement with her discussion of the strengths and weakness of each of the studies submitted in support of this application.

In brief, the sponsor provided analyses of the three principal Phase 3 studies using the agreed-upon primary endpoint, which was a pre-specified definition of the time to alleviation of major influenza-like symptoms. As discussed in the clinical review, it was anticipated that secondary endpoints and other approaches for analyzing the data would be important because of the subjectivity of the self-reported, symptom-based endpoint and because of probable confounding by the use of symptomatic relief medications.

Based on analyses of the primary endpoint, two of the three trials demonstrated a significant difference in time to symptom alleviation between zanamivir and placebo-treated subjects (1.5 days and 2.5 days in studies conducted in the Southern Hemisphere and Europe, respectively). Results of secondary endpoint analyses in both of these trials were consistent with the primary endpoint analyses, providing further support for the robustness of the findings from these trials.

In the largest phase III trial, conducted in the United States and Canada, the one-day difference between treatment groups did not reach statistical significance ($p=0.078$). Similarly, a phase II trial conducted in North America found a small non-significant difference in symptom alleviation between zanamivir and placebo-treatment groups (0.75 days). Despite lack of a statistically significant finding in the North American phase III study, several aspects of its results were compatible with a modest treatment effect, including numerical (if not significant) results in favor of zanamivir in analyses of the primary endpoint and various secondary endpoints (such as median days to alleviation without relief medication, investigator global assessment, and frequency of complications). Although suggestive, the secondary analyses need to be interpreted with caution because multiple analytic comparisons have been conducted. Therefore, I am in general agreement with the primary clinical reviewer's assessment that this adequately powered study was inconclusive in providing definitive evidence of efficacy.

The reason for the lack of a statistically significant finding in the primary endpoint analysis of the North America studies has been investigated through exploratory analyses and can not be determined from the available data. Speculation into possible reasons for the lack of a significant result in the largest phase III trial includes overall higher use of symptomatic relief medications, possibly less severe influenza, less familiarity with similar drug-delivery systems, or other factors. Despite the absence of definitive resolution to this question, I do not believe that the lack of a conclusive finding in the North American study negates the robust demonstrations of efficacy in the European and Southern Hemisphere studies, particularly given the inherent difficulties in conducting trials for this indication.

Overall, the totality of the data provides evidence that treatment with zanamivir confers a modest reduction in time to alleviation of influenza symptoms. The larger degree of benefit found in the

European study (2.5 day difference in symptom duration between zanamivir and placebo) was not replicated in any of the other zanamivir studies, and is likely to be an overestimate of the treatment effect that providers can reasonably expect.

This modest treatment benefit, approximately one-day on average, is likely to be clinically relevant when viewed within the context of an illness that lasts approximately 6-7.5 days among placebo recipients. Further, it should be noted that this estimate of treatment effect reflects a population-based "average"; the magnitude of benefit for a given patient is likely to depend on a number of host and viral factors, including: how soon the product is started after symptom onset, the age and medical history of the patient, baseline severity of influenza symptoms and the patient's proficiency in using the device. Factors that are expected to effect the likelihood of clinical benefit with this product are described in the labeling, and discussed further in section 4, below.

3. Applicability of foreign data

Considerable discussion at the February 24, 1999 Advisory Committee meeting focused on questions regarding the applicability of results from the non-U.S. trials to the population in this country. In general, FDA accepts foreign studies and may approve a drug based solely on their results provided that the data are clinically generalizable to the target population in the United States and the trials are conducted in a manner consistent with good clinical trial practice. In this circumstance, the results of the European and Southern Hemisphere trials are applicable to approvability for the United States, because there is no biological or pharmacokinetic reason to believe that drug-response in patients infected with similar types of influenza will differ between countries and because investigation of the clinical trial sites supported the integrity of the conduct of the foreign trials. Further, although the results of the North American study were not statistically conclusive, the numerical trends were consistent with the results of the foreign studies, and compatible with a modest treatment effect.

Additional support for antiviral activity in the U.S. population in particular is provided by the results of a community influenza prophylaxis study, conducted in 1107 university-based individuals. Although unreviewed by the division at this time, the report of this study suggests that zanamivir was effective in this population in reducing the frequency of influenza, compared to placebo (6% vs. 2% rate of infection in placebo and zanamivir groups, respectively). While the limited nature of the study population (otherwise healthy, younger individuals) makes this sole study an insufficient basis for approval of a prophylaxis indication, this study contributes support for the activity of this product against influenza when used in this country.

4. Describing the likely magnitude of clinical benefit

The zanamivir database, while generally supportive of efficacy, consists of studies that provide a range of expected treatment effect. The observed difference in the median time to symptom alleviation ranged from up to one day in the North American studies to 2.5 days in the European study. Further, retrospective subgroup analyses suggest that the magnitude of treatment effect differed based on patient age, baseline temperature and baseline symptom severity. Although these findings are based on analyses that are retrospective in nature, and limited by sample size, all

three principal studies suggested that patients ≥ 50 years of age were likely to derive more benefit from therapy than the overall influenza-positive population, and patients with lower entry temperature and less severe symptoms were less likely to derive benefit from therapy. Product labeling will provide information to assist health-care providers in their considerations regarding the role of antiviral treatment for an individual patient and the patient's likelihood of deriving benefit from therapy.

5. Other efficacy-related issues

a. Interpretation of symptoms reported after initial alleviation

The issue of how to analyze and interpret influenza symptoms occurring after initial alleviation (i.e., after the primary endpoint was reached for a given individual) was raised in the Biometrics presentation at the Advisory Committee meeting. Following the Committee's discussion about the clinical interpretation of this observation, the sponsor was asked to provide further analyses to address whether there was evidence that symptom occurrence after initial alleviation was a more frequent observation in zanamivir-treated patients compared to placebo.

These additional analyses suggest that while patients did occasionally report moderate-to-severe symptoms after reaching the alleviation endpoint, symptoms were reported in both treatment groups in similarly low frequencies. It is my interpretation that these symptom reports reflect the waxing and waning nature of influenza resolution, and do not represent a "rebound" phenomenon after antiviral treatment. It is of interest to note that the rimantadine database raised a similar review issue and a similar conclusion about its lack of clinical significance in the adult studies was reached. Both of these applications demonstrate the difficulty in studying and defining an analytic endpoint for this highly subjective illness.

b. Efficacy in higher risk individuals

Evidence for efficacy in a medically higher risk population was not demonstrated in this application. A total of 217 patients enrolled into the three principal trials were defined as "high risk". This relatively small population was heterogenous in nature, and included patients > 65 years of age, or those with a variety of respiratory, cardiovascular and other medical conditions. Non-significant differences of 2-3 days in the primary endpoint in favor of zanamivir treatment were found in the Southern Hemisphere and European studies; a non-significant difference of 0.25 days in favor of placebo was found in the North American study. In general, no conclusions about zanamivir's efficacy in this subpopulation can be reached based on these analyses. The labeling provides a statement that efficacy in higher risk individuals has not been established and provides guidance on appropriate use and possible adverse effects in those with underlying respiratory disease (see section 7, for further discussion of safety issues). The sponsor has committed to providing more information on safety and efficacy in higher risk individuals in Phase IV.

c. Prevention of complications

The data in this application does not provide compelling evidence that zanamivir treatment prevents influenza-associated complications, such as pneumonia, other infections requiring antibiotic treatment, and others. The incidence of complications or antibiotic receipt was numerically higher in placebo-treatment groups among all influenza-positive patients in the three principal studies. However, among influenza-positive high-risk patients, the rate of complications or antibiotic receipt was numerically higher in placebo recipients in the Southern Hemisphere and European studies, only. Therefore, the small sample size does not permit a conclusion about the role of zanamivir treatment in preventing complications of influenza. The labeling provides a statement that an impact on prevention of complications has not been established.

6. Evidence supporting efficacy against Influenza B

There are no currently approved products with activity against influenza B. *In vitro* data suggest that influenza virus types A and B should both be susceptible to neuraminidase inhibition, although potentially to different degrees. Conversely, it is not expected that zanamivir will have activity against influenza C virus.

Please refer to the microbiology review for a discussion of the preclinical evidence to support zanamivir's activity against influenza B. Clinical support for zanamivir's activity against influenza B is provided by the results of an influenza B challenge study in which intranasal zanamivir was administered fours hours prior to inoculation (a second challenge study provided inconclusive results) and by results of the principal phase III studies. In these trials, approximately 11% of influenza-positive patients had infection with influenza B, which is consistent with expectations of a lower rate of naturally occurring influenza B. Although the sample sizes were inadequate to definitively establish (with statistical confidence) comparability of treatment effect between patients infected with influenza A and influenza B, numerical results were generally similar. Therefore, based on the cumulative evidence, it appears reasonable to conclude that zanamivir has antiviral activity and probable clinical efficacy against both influenza A and B viruses. However, the label will include precautionary language that there is less evidence to support its efficacy in the setting of influenza B infection. Additional information about zanamivir's efficacy for treatment of influenza B infection has been requested as a Phase IV commitment.

7. Safety

The submitted safety database contained information on 2289 patients treated at least twice daily (including several hundred patients treated four times daily during a phase 2 study) for five days with zanamivir in phase 2 and phase 3 studies, and 623 subjects treated once daily for four weeks (as part of prophylaxis and vaccine interaction studies). More limited information on higher dose exposure is available in 20 subjects who received 600 mg of intravenous zanamivir twice daily for 5 days. The size of this database was discussed with the Division during development, and there was agreement that this represented a reasonable size for this indication. Additionally, while the size of this database is insufficient to exclude rare adverse events, it provides a considerably larger basis than that available prior to the approval of either amantadine or rimantadine. Overall, the

safety profile of this product is acceptable for general use in healthy individuals. However, special precautions are warranted if used in individuals with underlying respiratory disease.

Safety in patients with underlying respiratory disease is the only potentially significant safety concern that was identified by the Advisory Committee and clinical reviewers. This issue was initially raised by the finding of reduced FEV1 following zanamivir (but not placebo) treatment in one out of 12 mildly asthmatic subjects in a phase I study designed for the purpose of assessing safety in this population. Following the team's request for more information on this issue, the sponsor provided preliminary safety data from an ongoing study of the safety and efficacy in patients with asthma or COPD (NAI30008). In a preliminary analysis of 148 patients, there were more frequent declines in FEV1>20% from baseline in patients in the zanamivir group at day six (15% vs. 6% placebo) and at day 28 (10% vs. 3% placebo).

In consultation with colleagues in the Division of Pulmonary Drug Products, consensus was reached that this issue can be adequately addressed in the label and does not pose a barrier to approval. Accordingly, the label will provide precautionary information about the potential risk of bronchospasm in patients with underlying respiratory disease, the lack of data to support its efficacy in this population, and clinical directives regarding patients instructions should bronchospasm occur. Additionally, the sponsor has committed to additional investigation of this issue in Phase IV, which will include submission of the final results of study NAI30008, conduct of an additional study to evaluate pulmonary function, and active post-marketing surveillance efforts.

8. Emergence of resistance

Efforts to evaluate the emergence of viral resistance to zanamivir have been hampered by the lack of a reliable cell-culture-based test. Currently available information on resistance is based on assays of neuroaminidase activity, for which the clinical relevance is not well established. Information derived from this methodology suggests that resistance can emerge both *in vitro* and clinically (based on the report of an immunocompromised individual who developed influenza B resistant virus following treatment with nebulized zanamivir). Although the collective data provided do not suggest that resistance emerges routinely, post-marketing surveillance of resistance is essential. The sponsor has committed to development and implementation of a resistance surveillance program; as part of this effort, the sponsor will continue to explore the feasibility of development of a cell-culture-based assay for viral susceptibility and resistance to zanamivir.

9. Drug-delivery related issues

This application provides a novel drug delivery approach for outpatient treatment of a viral infection; similar devices and blister-packaged medications are already approved for treatment of asthma. Use of this system during an acute, brief illness raises the question of how quickly patients will develop proficiency in self-administration. Prior to prescription, health-care providers will need to assess whether a given patient is likely to develop proficiency in a reasonably rapid manner. In order to increase the likelihood of effective use, product labeling

recommends that health-care providers demonstrate use of the product whenever possible.

The sponsor has committed to development of instructional materials for providers and patients, and has further committed to the conduct of a labeling comprehension study in North American patients with active influenza with the intent of assessing and improving patient instructions for use.

10. Phase IV commitments

The sponsor has agreed to phase IV commitments that will provide additional information on the following issues: use of the Diskhaler device and improvement of instructions; safety and efficacy in patients with underlying respiratory disease, high-risk patient groups, pediatric patients and North-Americans in general; safety and efficacy for interruption of influenza virus transmission and prophylaxis; safety and efficacy in treatment of influenza B; consequences of re-treatment; impact on viral shedding; resistance surveillance and assay development; educational material development; and preclinical concerns (including immunotoxicology, juvenile toxicology, and manufacturing questions).

In conclusion, this application provides adequate information that zanamivir is safe and effective for treatment of uncomplicated influenza when prescribed under the conditions described in the product labeling. The sponsor has committed to appropriate phase IV endeavors to further investigate optimal and safe use of this product, for treatment and related indications.

I would like to personally commend the entire zanamivir review team for their efforts during the review of this application's complex preclinical and clinical database.

There are no additional outstanding regulatory issues at the time of this action.

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cc:
NDA 21-036
HFD-530/Styrt/Kukich/Birnkrant
HFD-104/Murphy

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