

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 Styrts 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 four 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.

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

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

 /S/
Heidi M. Jolson, M.D., M.P.H.
Director, Division of Antiviral Drug Products

**APPEARS THIS WAY
ON ORIGINAL**

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

COMBINED MEMORANDUM TO THE NDA

NDA: 21-036

Drug and Indication: Relenza® (zanamivir dry powder for inhalation) for treatment of influenza A and B viral infections

Dose: 10 mg twice daily for five days for use with the DISKHALER® Inhalation Device

Applicant: Glaxo Wellcome, Inc.

Date of Submission: October 26, 1998

Date of Memorandum: July 15, 1999

The applicant has requested approval for zanamivir, an inhibitor of influenza virus neuraminidase activity, administered by oral inhalation using a lactose powder vehicle with the DISKHALER® inhalation device for the treatment of influenza A and B viral infections. In support of this indication, the applicant has submitted the results of phase 2 and phase 3 trials conducted in the North America, Europe, and Southern Hemisphere during respective influenza seasons. The principal studies enrolled 1588 patients ages 12 years and older with uncomplicated influenza-like illness, with symptoms present for two days or less. Of 1164 patients with confirmed influenza, 89% had influenza A and 11% had influenza B.

Based on discussions between the applicant and the Division, the primary endpoint was defined as time to alleviation of major influenza-like symptoms, which included temperature below 37.8⁰ C, feverishness symptom score of zero, and symptom scores no greater than mild for cough, headache, myalgia, and sore throat, all maintained without worsening for the subsequent 24 hours. Because of the subjectivity of the endpoint and concerns that use of relief medications could confound measurement and interpretation of this endpoint, throughout the development process the Division has considered it essential that certain secondary endpoints provide information supporting the conclusions for efficacy.

A total of 2289 patients, ages 12 and older, received zanamivir across all studies and are included in the safety database.

This application was presented at a meeting of the Antiviral Drug Advisory Committee on February 24, 1999. Based on the presented information, the Committee voted against recommending approval at that time. The concerns raised at the meeting were associated with lack of demonstrated treatment effect in the North American study, magnitude of the

treatment effect, a need for more information regarding patients with underlying pulmonary disease and high-risk patients, and recurrence of symptoms following treatment. These concerns and other major issues of this NDA have been thoroughly discussed in the medical officer's review. It should also be noted that there were some misperceptions by some members of the committee that only domestic studies were acceptable for making drug marketing claims in the United States. Despite statements of correction from FDA participants, this concept recurred in various forms throughout advisory committee discussions.

The Division has considered the totality of the data from three prospective phase 3 clinical trials conducted in North America, Europe, and the South Hemisphere, as well as other supporting data contained in the NDA. Although the treatment effect appears limited and there is less evidence for efficacy in influenza B than in influenza A, when all efficacy and safety data are reviewed together, the results support the approval of zanamivir for the treatment of uncomplicated acute illness due to influenza. However, several aspects of this drug's development and approval merit comment:

Summary of data in support of efficacy

Treatment effects were not consistent across the principal phase 3 studies. The largest phase 3 treatment study conducted in the North America failed to demonstrate a convincing treatment effect. However, the other two principal trials demonstrated clinically meaningful and statistically significant treatment effects. The differences between studies were not conclusively explained, however, the variable magnitude of treatment effect may have depended on the amount of symptomatic relief medication used and familiarity with the use of device. The efficacy results calculated by the applicant are provided in the following table.

Difference between placebo and zanamivir, primary endpoint

	NAIB3001 (Southern Hemisphere; n=455, Flu + 321, high-risk 76)	NAIB3002 (Europe; n=356, flu + 277, high-risk 32)	NAIA3002 (North America; n=777, flu + 569, high-risk 109)
Median days to alleviation (flu +)	P 6.0 days, Z 4.5 days, p=.004	P 7.5 days, Z 5.0 days, p<.001	P 6.0 days, Z 5.0 days, p=.078
Median days to alleviation (all randomized subjects)	P 6.5 days, Z 5.0 days, p=.011	P 7.5 days, Z 5.0 days, p<.001	P 6.0 days, Z 5.5 days, p=.228
Median days to alleviation (high-risk)	P 8.0 days, Z 5.5 days, p=.048	P 11.5 days, Z 9.0 days, p=.178	P 6.5 days, Z 7.5 days, p=.710
Median days to alleviation (high-risk, flu +)	P 8.3 days, Z 5.0 days, p=.161	P 11.5 days, Z 9.25 days, p=.21	P 6.0 days, Z 6.25 days, p=.886
Median days to alleviation (flu negative)	P 7.0 days, Z 6.75 days, p=.486	P 7.0 days, Z 5.25 days, p=.551	P 5.0 days, Z 6.0 days, p=.712

Despite limited efficacy in the North American study, the Division determined that this application provides sufficient evidence of efficacy because:

- When a disease is usually self-limited and of a short duration (days) it is a more difficult task to demonstrate a difference between the treatment groups. The efficacy of this product, based on the previously noted efficacy parameters and the understanding that influenza is a self-limited illness, has been demonstrated in two well-controlled trials conducted in Australia, New Zealand, South Africa, and Europe. Although these data are from foreign studies, they were carried out in populations that would not be expected to differ substantially from the US population, in characteristics of influenza illness, or access to widely accepted aspects of general medical practice.
- The third phase 3 treatment study conducted in North America is inconclusive in itself; taken together with the other studies, it is compatible with a modest effect.
- The phase 2 studies, although smaller and/or using different preparations of the drug are also compatible with a real but modest treatment effect in both North American and non-North American populations.
- The treatment effect was not clearly different in patients with influenza A and B; however, because of a smaller number of patients with influenza B enrolled into these trials, there was less evidence in support of efficacy of zanamivir in the treatment of influenza B.
- Although not a part of the formal review of this NDA for a treatment indication (only safety data were presented at the Advisory Committee meeting), preliminary results from the community prophylaxis trial conducted in the United States, involving over a thousand patients, also provide support of zanamivir's activity against influenza A in North America.
- Some patients reported influenza-like symptoms after the primary endpoint was reached. Assessment of symptom rebound or recurrence has been addressed by the analysis of time to alleviation without subsequent rise of symptoms and by additional analyses such as the analysis showing that the proportion of diary cards indicated "non-alleviated" after the primary endpoint did not differ substantially between the treatment groups.

Although no direct comparison can be made with drugs reviewed on the basis of different study designs, the marketing applications for the two drugs previously approved for influenza A treatment (amantadine and rimantadine) provide some useful context regarding the difficulties of performing influenza studies and interpreting the results. These two drugs were approved on the basis of much smaller studies. The study participants were from limited populations. A variety of endpoints were used, which

were not always clearly defined prospectively. In addition, the two approved drugs for the treatment of influenza are active only against influenza A.

Tolerability of this product during the conduct of the clinical trials was generally acceptable; overall, reported adverse events were similar between zanamivir and lactose inhaled powder.

The concern about the safety of this product in high risk patients was also raised during the Advisory Committee meeting. The preliminary safety data from the ongoing treatment study in asthma/COPD patients suggest that some patients with underlying airway disease may experience decreases in FEV1 in connection with inhaled zanamivir administration. This information is incorporated in the Precautions section of the labeling for zanamivir and thereby, describes the potential risks for this patient population.

Public Health Considerations

Influenza infection causes significant morbidity and mortality each year. During the 1998-1999 influenza season in the United States, the percentage of deaths from 122 reporting cities exceeded the epidemic threshold for 12 consecutive weeks according to the Centers for Disease Control and Prevention influenza summary update.

Clearly, the armamentarium for the treatment of influenza is lacking. As of 1993, only two medications, amantadine and rimantadine have been approved for the treatment of influenza A. The lack of new influenza medications became more evident recently when a strain of influenza virus that was previously known to infect only birds was associated with human disease. At least seven confirmed, unusually severe cases of influenza A due to the H5N1 strain of influenza virus were identified in Hong Kong between May and December of 1997.

Infection with a new virus strain raises significant public health concerns. A new virus has the potential to cause global disease in the form of a pandemic. To prepare for such a challenge, it is important to have new therapies available. Ideally, these new therapies would have antiviral activity against multiple influenza A strains, as well as influenza B, and a different side effect and resistance profile than currently marketed products.

Neuraminidase inhibitors, such as Relenza (zanamivir for inhalation) represent a new class of antiviral agents for the treatment of influenza. The neuraminidase enzyme is involved in the prevention of aggregation of influenza virus particles on the surface of infected cells. The proposed mechanism of action of zanamivir for inhalation is via inhibition of viral neuraminidase with the possibility of alteration of virus particle aggregation and release.

With regard to resistance, the extent of the data contained in the NDA package are insufficient to fully characterize the risk of emergence of resistant virus with clinical use. However, the applicant has committed to the development and implementation of a resistance surveillance program.

[Redacted]

It is expected that these issues will be satisfactorily addressed by the time of the regulatory action.

[Redacted] /S/ [Redacted]

Stanka Kukich, M.D.
Medical Team Leader, HFD-530

[Redacted] /S/ [Redacted]

Debra B. Birnkrant, M.D.
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cc:
NDA 21-036
HFD-530 /HJolson/DBirnkrant/BStyrt

APPEARS THIS WAY
ON ORIGINAL

DEC 29 1998

MEDICAL OFFICER CONSULT		
NDA #:	21-036	
PRODUCT:	RALENZA (ZANAMIVIR)	
CATEGORY OF DRUG:	INFLUENZA A AND B ANTIVIRAL AGENT	
ROUTE OF ADMINISTRATION:	INHALED VIA A DRY POWDER INHALER	
SPONSOR:	GLAXO WELLCOME	
CONSULT BY:	ROBERT J. MEYER, MD, MEDICAL TEAM LEADER	
CONSULT DATES	DOCUMENT DATE	10-8-98
	CONSULT SUBMITTED:	11-4-98
	RECEIVED BY REVIEWER:	11-10-98
	REVIEWED:	12/23/98

Introduction:

This consultation is for a novel antiviral drug product specifically targeted at the viral replication of influenza A and B viruses. It is intended for use as an oral inhalation drug product with the rationale that the primary site of viral replication during influenza is the respiratory epithelium. An additional consideration in this rationale is that the drug is apparently poorly bioavailable from the gastrointestinal route (<2%).

Because this is the first product of its kind (an inhalational dry powder formulation of an antiviral for influenza), DAVDP has requested input from DPDP related to the pulmonary/respiratory aspects of the application. It is noteworthy that this product utilizes the Rotadisk via Diskhaler device that in a slightly different configuration was previously approved as a part of the Flovent Rotadisk NDA (20-549). Like many DPIs, this formulation utilizes lactose as the drug carrier. Like the Flovent DPI, this product utilizes a 4-blister Rotadisk, with a daily dose consisting of two blisters inhaled twice daily - or 1 disk per day. The blisters come in a tube that carries 5 blister disks, or 5 days treatment (the recommended duration).

Materials Reviewed:

- ISE volumes of the NDA (v. 134 and 135 of 162 of NDA 21-036)
- ISS volumes of the NDA (v. 136 and 137 of 162 of NDA 21-036)
- Proposed labeling (including PPI)

Structure of Consultation Report:

This consult begins with a general discussion of some of the relevant issues in the development and approval of an inhalation drug product (irrespective of the proposed indication). It then enumerates and discusses specific issues and areas of concern related to the zanamivir inhalation drug product. Note that ongoing discussions have been conducted between the consulting Medical Officer from DPDP and the reviewing Medical Officer in DAVDP. Although some of the issues discussed below have previously been communicated, they are included in this review for documentation purposes.

Note: Upon receiving this consultation, please feel free to contact HFD-570 (Dr. Robert Meyer) for any further input or for any clarifications.

General Discussion:

Dry powder inhalers (DPIs) have become increasingly common as devices for administering respiratory drugs. In addition to pulmonary indications, dry powder formulations for inhalation are being developed for delivery of systemic medications (such as insulin). For DPIs, the use of lactose as a carrier offers the advantages of being well established clinically, since lactose has been utilized for many years in approved dry powder inhalation formulations such as the Intal Spinhaler and the Glaxo Wellcome product Ventolin Rotocaps (as well as many more recent products).

When lactose is used as a carrier, particle sizing of the lactose is ordinarily targeted so that it is sufficiently large that little is inhaled into the lungs, but rather remains in the device or impacts in the oropharynx. Dry powder inhalers (DPIs) usually depend on patient inhalational force to dissociate the active micronized drug from the lactose carrier. For the DPI to be effective in a wide range of patients, therefore, the DPI device must deliver efficiently over a wide range of inspiratory efforts that patients of varying ages and underlying lung diseases might generate. It is often stated in medical literature that the elderly and very young (e.g., < 4 years of age) may be poor choices for DPI therapy due to this necessity of patient effort for proper disaggregation and medication delivery (although this opinion is not always based on specific data).

Another potential problem for lactose-based DPIs commonly cited in literature is their susceptibility to the deleterious effects of humidity. The dissociation of active drug from the lactose carrier is critically dependant on the hydration state of the lactose particles in the formulation. This concern has been borne out for some products that DPDP has reviewed, with the stability of the product – even in blister doses – limiting the in-use time for the product. However, clearly the humidity issue is mostly a concern for DPIs intended for chronic use and likely to have long in-use periods (i.e., weeks to months).

I. GENERAL CONCERNS

With regard to general concerns related to an inhaled anti-influenza product, there are several observations we would make regardless of the specific content of the NDA:

- (a) This drug, although targeted at a disease with systemic manifestations, is intended by the sponsor to act locally within the respiratory tract epithelium, since this is apparently the major sight of viral replication in influenza A and B. DPDP has in the past required any *specific* topical effects claim to be based on data showing that the drug administered topically is more effective than a systemic dose resulting in the same level of systemic exposure. In DPDP's paradigm, if the sponsor fails to prove the effect is topical, the product may be clinically approvable, but any specific labeling claims that it indeed works topically are not permitted.
- (b) Influenza can be a major precipitant of asthma and COPD exacerbations, so the patient population with chronic lung disease would likely be an important population for treatment and/or preventive use of this product. It would therefore be important for the sponsor to address specific safety and tolerability of an inhaled anti-influenza product in a

bronchospastic population not only when they are stable, but during acute influenzal illness. It does appear that the sponsor attempted to address both of these issues in their application and this will be commented upon later in the consult.

- (c) Since DPIs can be somewhat complex devices (and the Rotadisk perhaps more so than most), it would be important for a product that will be used short-term and sporadically by a DPI naïve population to have instructions that are quite clear-cut and that lead to effective use. Ideally, the sponsor should provide evidence of such outside the clinical trial setting, where well-versed investigators carefully instruct, observe, and coach patient use.
- (d) The CMC staff working with DAVDP should assess the in vitro dose delivery characteristics of this product over varying flow-rates. Glaxo Wellcome should also be asked to provide data on what flow-rates patients – including patients with impaired airways – can generate through this device, so that some assurance that the product delivers satisfactorily over the range of likely flow rates can be obtained.
- (e) The duration of recommended use and the package size of the refills will be important for relating to the stability data developed by the company. As detailed above, lactose-based DPI formulations are susceptible to humidity, once any secondary packaging (i.e., overwrapping such as the polypropylene tube) is removed. The Flovent Rotadisk, for instance, should be used within 8 weeks of opening of the tube in which it is packaged.

II. PROPOSED LABELING

Below are several comments regarding the proposed package insert, which was reviewed prior to the review of clinical data:

- (a) In the Description section, there is no statement of what dosing is actually delivered from the device during in vitro testing or in vivo use. DPDP generally requests that sponsors include such data for DPIs in the description section, since it is unlikely that the 5 mg of zanamivir contained in a blister is actually fully delivered from the device. This information, if based on in vitro testing, should state the in vitro conditions used to quantify the delivered dose (e.g., 30 L/min flow rate).
- (b) For the purposes of internal CDER consistency, the established name for this product should be zanamivir powder for inhalation. For instance, the name of the fluticasone product is Flovent Rotadisk (fluticasone propionate powder for inhalation).
- (c) Although not our purview, I am puzzled by the description in the 'mechanism of action' subsection that zanamivir acts extracellularly. This seems to suggest that it blocks influenza virus entry into epithelial cells, which does not seem to be the case.
- (d) The 'mechanism of action' subsection has what is tantamount to a topical effects claim. The sponsor states that "the efficacy of topical administration of zanamivir to [the respiratory epithelium] has been confirmed in clinical studies." As previously stated,

DPDP has required that any overt claim of topical effect (rather than a general claim of efficacy and safety for the inhaled route) should be substantiated with data that truly examines the relative efficacy of the topical route vs. systemic administration. We note that the PK data cited in the labeling includes an estimate of systemic bioavailability via this inhaled product of between 4 to 17%. Glaxo Wellcome has shown repeatedly in other development programs that the Diskhaler device delivers into the lungs approximately 12 – 15% of a dose contained in a blister (and such data are cited in the PK section of the labeling for this product as well). Finally, the oral bioavailability is $\leq 2\%$ and therefore any swallowed portion of a dose would contribute negligibly to any estimate of systemic bioavailability. One can infer from these pieces of information that the large majority of the inhaled dose is subsequently absorbed systemically. It is at least plausible (though not necessarily probable) that the approximately 1200 mcg of drug delivered to and absorbed from the lungs per dose may act systemically to treat influenza infection, rather than the effect being truly topical. Again, to clearly support a claim of topical effect, DPDP believes the sponsor should conduct a trial in which a systemic dose (oral or parenteral) is administered that achieves comparable serum levels as those noted following inhalation, comparing the efficacy of that systemic administration in parallel to the inhaled formulation.

- (e) The discussion of the asthma data in the 'special populations' subsection of the labeling should be revised to reflect data available from asthmatic patients dosed in the phase 3 clinical trials, if possible. The 'safety study' in 13 mild-to-moderate, stable asthmatics does not provide a firm basis for labeling purposes with regard to the safety and tolerability of the product in a wide, disparate asthmatic population. We make this statement based on the small number of relatively mild patients entered into this study. Further, this study did not address the more relevant concern as to how asthmatic patients with acute influenza (and therefore with even more hyperreactive airways) tolerate the medication.
- (f) We note that the sponsor is only seeking to gain a treatment indication at this time and not an indication as a preventative. This simplifies issues related to stability of the Rotadisks once removed from secondary packaging, since the intent is for patients to use all 5 disks within 5 days of initiating therapy. When a preventive indication is sought, however, such issues should be fully addressed by the sponsor.
- (g) In the "Patient Instructions for Use," there is no precaution not to utilize this Diskhaler for Flovent Rotadisk administration or visa-versa. Since presumably there are no *in vitro* or *in vivo* data related to the effects of utilizing the Flovent Diskhaler (with any accumulated drug substance in the device airstream) with zanamivir Rotadisks nor visa-versa, there should be a caution that the zanamivir Rotadisk should be administered only with the Diskhaler provided and that the Diskhaler provided should not be used with Rotadisks other than those containing zanamivir (note, DPDP should also address this in the Flovent labeling, if and when zanamivir is approved).
- (h) The instructions on device use for the patient appear to be reasonably worded, though

lengthy. We make the following points for your consideration regarding the instructions:

- (i) In step 1, bullet 5, the instruction should state to push the white tray *all the way* in until it clicks firmly into place, since the device also clicks just after reseating the mouthpiece.
 - (ii) In the bolded statement at the beginning of step 2, the second sentence should be revised to assure that patients keep the Diskhaler level throughout the step 2 and step 3, that is, during the puncturing and inhalation process.
 - (iii) Step 1 ends with the instruction to replace the cover, yet step 2 does not state to remove the cover. It should, because the instructions as written cannot be accomplished with the cover still on the Diskhaler.
 - (iv) The cautionary statement that patients should be sure the mouthpiece is free of foreign objects prior to each use should be included in step 2 instructions, rather than at the end. DPDP has seen adverse event reports for MDI products of coins and other foreign objects inhaled when patients have kept inhalers without using the cover and have not checked the mouthpiece prior to inhalation. This is not a trivial recommendation.
 - (v) It is unclear whether the sponsor ever tested the instructions in a DPI naïve population for clarity and intelligibility. As previously stated, the Diskhaler/Rotadisk DPI is a complex device and will likely have a significant degree of sporadic use in patients unfamiliar with inhalers in general and DPIs specifically. Considering all that, DPDP feels it is important to ascertain with the sponsor whether any such comprehension and use studies have been conducted, and if not, perhaps to request one.
- h) There are no instructions for the patient regarding cleaning of the Diskhaler device. While we note that currently the product is proposed only for treatment and not prevention, if a preventive claim is later sought, the sponsor will need to address proper maintenance and/or cleaning of the device.

III. ISSUES / COMMENTS FROM THE ISE REVIEW:

- a. On page 18 of ISE (vol. 134), there is a definition of a "high risk" pulmonary patient as one who requires regular medication for their pulmonary disease. We are not aware of any data in the medical literature that would corroborate this definition. More over, it is not clear what "regular" means for these purposes, nor whether these patients were significantly diseased in terms of their lung function / disease severity. If this is the only definition by which the sponsor has done subset analyses for efficacy and for safety, these analyses may be of relatively little use in drawing definitive conclusions regarding the efficacy and safety of this product in patients with significant lung disease. This is a concern since the only controlled tolerability study in respiratory patients was small

(n=13) and enrolled relatively mild asthmatics. It is a further concern since high-risk lung patients would be high amongst those who might be considered for a treatment or prevention of influenza.

- b. In the discussion of common protocol features on page 15 of the ISE (vol. 134) there is a statement that patients with unstable concomitant diseases were excluded from these trials. The definition of unstable patients indicates that those patients needing significant increases or changes in their medications were to be excluded. This raises the concern that an important group of asthma / COPD patients may have been excluded due to influenza-induced worsening of their airways disease (with there potentially being a need for either increased use of bronchodilators or the addition or increase of antiinflammatory medications in this setting). If it is indeed the case that such patients who's respiratory disease worsened with the onset of influenza, this raises both a further question about the safety data. The safety concern is that if such patients were excluded, the existing safety database may not be adequate to provide sufficient data to assure the tolerability of the zanamivir formulation in patients with destabilized airways disease. Both of these questions are important since patients with respiratory compromise would be likely recipients of a drug to treat influenzal illnesses.
- c. If we place concerns over appropriate severity aside, it does appear that the sponsor enrolled a reasonable number of "respiratory" patients to allow some confidence in judging the formulation's tolerability and safety outside of the small clinical pharmacology/safety trial, as there were 132 subjects included in the 3 main treatment trials (NALA3002, NAIB3002 and 3001) listed as having a respiratory condition. This accounts for approximately 8% of the 1864 subjects in these trials. However, regarding efficacy, there is a rather unimpressive 0.75 day difference in median time to symptom alleviation for these 132 patients, compared to the range of 1.0 – 2.5 days seen for the overall population in these three trials. While this may simply be due to chance variation arising from a small, post-hoc subgroup analysis, there remains the concern that this diminished efficacy could signal a patient-disease-drug interaction in COPD/asthma patients. One could speculate, for instance, that the delivery characteristics of the drug in patients with airways disease are less favorable in respiratory-impaired patients than in patients with normal airways, either due to diminished dosing from the DPI itself or due to changes in deposition within the pulmonary system. This point, if not otherwise addressed by existing data, may need further study.
- d. In tracking pulmonary complications of influenza as a reflection of efficacy, it appears that active treatment did convey some advantage. If one pools the data from the ITT population of the 3 major efficacy trials, the following was observed:

Complication:	Placebo	Zanamivir
Pneumonia	18	8
Airways disease exacerbation (COPD and Asthma)	13	6
Bronchitis	52	41
Resp. Failure	1	0
Other	17	23
TOTAL	101	78

There is an apparent numerical advantage for zanamivir-treated patients overall and in all of these categories of influenza-related respiratory processes, except for "other." Note, however, that it is not clear from the ISE what diseases/diagnoses the term "other" encompasses, but that should be assessed to assure that there is no hidden safety signal (i.e., a drug-related adverse event) arising within those data. An additional caveat is the concern that unstable airways disease patients may have been removed from these trials because of needing additional medications, as mentioned above. One hopes that if that occurred, the patients were still included in the above data set. That is not clear from the data in the ISE, however.

Overall, these data on pulmonary complications offer some insight not only on safety, but also on the efficacy of the product, since if zanamivir effectively treats influenza, by inference it should prevent secondary pulmonary complications.

IV. ISSUES / COMMENTS FROM THE ISS REVIEW:

- a. We note that in the pre-clinical testing discussion, there were some minor respiratory tract findings (epithelial hyperplasia in the 26 and 52 week dog studies in all zanamivir-exposed dogs and increases in size and numbers of alveolar macrophages in all dosage groups in the 104 week rat study). These findings would ordinarily raise some clinical concerns in DPDP if they were present in toxicology studies for chronically administered pulmonary drugs, since these are not monitorable changes in clinical trials. However, given that this NDA is for a 5-day treatment period, and not prolonged prophylaxis, these findings are not as relevant for this indication (presuming there were shorter preclinical studies that showed no such toxicities).
- b. Table 73 of the ISS represents the adverse event data for respiratory patients deemed as "high risk." Focusing on the respiratory events, it is notable that there were fewer complaints of asthma, cough and bronchitis in active treatment patients than in placebo, since all of these events could occur as a result of intolerance to the formulation. Rather, these data suggest not only reasonable tolerability for the formulation, but that the active drug may have prevented some of these events. That noted, it is at least a bit curious that in this population, there were only 4 pneumonia cases documented and they were all in active 10 mg BID treated patients. Although this is not a definitive signal of any meaningful problem, it does perhaps somewhat temper the conclusion that the former data clearly help support efficacy, in addition to tolerability. Note that the ENT data looking at other events that might reflect tolerability from this same population (e.g.,

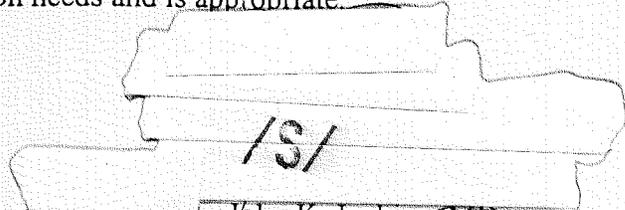
pharyngitis, throat pain,...) do not show any disparities suggesting problems with tolerability.

- c. The specific safety data from study C94-085 (the clinical pharmacology study in 13 mild to moderate asthmatics) do not show any clear signals of problems with tolerability of the active formulation compared to lactose alone. In fact, in the categories of chest tightness, low spirometry readings (FEV₁) and wheezing, there were numerically more cases in the placebo group than in active treatment (see below). The caveat remains, however, that while this study may have allowed the sponsor some confidence to proceed into the clinic, due to limited size and the stable population chosen, it offers little assurance of tolerability in acutely unstable asthmatics or COPD patients and does not in our view provide a basis for labeling statements.
- d. Since the placebo inhaler contains lactose, there are no data in the ISS to speak to whether the full formulation led to a relative increase in respiratory adverse events (cough, chest tightness, ...), only on the contribution of active drug relative to the carrier alone. While this may be true of most DPIs development programs, it is more of an issue for a treatment modality intended for use in the treatment of an acute respiratory tract pathogen, where the disease may render subjects more susceptible to adverse effects of an inhaled, lactose-based formulation. The sponsor argues that the prophylactic trial data best addresses the issue of lactose tolerability, since there is less acute disease to confound the interpretation. In these trials, the upper respiratory symptoms were no more prevalent with active treatment than with placebo. However, these data still do not adequately elucidate the tolerability of the formulation compared to no treatment. These data show that 27% of subjects complained of cough during this 28-day trial, but the majority of episodes were shorter than 5 days and few patients discontinued due to cough. These data support the conclusion that if cough does occur related to lactose alone, it is not severe and it is not long prolonged in most subjects. However, it is still possible that the lactose itself (and hence the full formulation) would be more irritating and problematic in more acutely ill patients.
- e. A review of the case narratives does not raise any clear signals from the pulmonary perspective. The one respiratory death on active treatment (A0062551 – NAIA3003) was culture positive for influenza A and has the character more of treatment failure than of an adverse event related to treatment. Likewise, the cases of serious adverse respiratory events (mostly secondary, lobar pneumonias) reported were consistent with treatment failure, rather than a drug-related event.
- f. A review of lower respiratory adverse events leading to study discontinuation (table 48 of the ISS on page 361 of volume 136) showed that overall the rate was no higher in active treatment than in placebo. Also of importance is that this rate (<1%) was not high for either placebo or active treatment, which argues for overall reasonable pulmonary tolerability of the lactose and the full formulation. However, it is notable that the only patients who withdrew specifically for cough were receiving active drug (3 patients total out of the 2289 exposed; with 0 patients out of 1520 withdrawing from placebo). These

clearly are not the kind of numbers which allow confident statements that this represents an observation difference from chance alone. However, if real, this small increase in drop-outs due to cough does not appear to represent an unreasonable safety concern for inhaled zanamivir.

If you have other concerns or questions as the primary review progresses, please feel free to call Dr. Meyer at 827-1050. We will plan to attend the advisory committee meeting for zanamivir and will participate at what ever level your division needs and is appropriate.


/s/
Robert J. Meyer, MD
Medical Team Leader, DPDP
12/23/98


/s/
John K. Jenkins, MD
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12/23/98

APPEARS THIS WAY
ON ORIGINAL