GLAXOSMITHKLINE

Sponsor Briefing Information

RELENZA® (zanamivir) Inhalation Powder
NDA 21-036

Review of Antivirals for Home Stockpiling Use for Pandemic Influenza and Development Plan for Relenza MedKit

FDA Antiviral Drug Products and Nonprescription Drug Products Advisory Committee Meeting

October 29, 2008

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1. INTRODUCTION

1.1. Purpose of Briefing Information

This 'Briefing Information' has been prepared by the Sponsor, GlaxoSmithKline, for review by members of the Antiviral Drugs Advisory Committee and the Nonprescription Drugs Advisory Committee in preparation for the Advisory Committee Meeting scheduled for October 29, 2008. The purpose of the Meeting is to explore the concept of home stockpiling antivirals for pandemic influenza, as requested by the Biomedical Advanced Research and Development Authority (BARDA) of the US Department of Health and Human Services [US HHS, 2008], and to discuss the proposed development plan for a "MedKit" containing Relenza® (zanamivir) Inhalation Powder, that is intended for this purpose. It is the common goal of GSK and FDA that this Briefing Information, together with the Briefing Information prepared by the FDA Review Team, will provide the basis for a thorough discussion of the many and complex issues facing the development of a zanamivir home stockpiling MedKit.

The content of this document will provide background information on pandemic influenza and the utility of antivirals and zanamivir for the control of the spread of a pandemic strain, the rationale and recommendations for stockpiling antivirals for pandemic preparedness, and the stockpiling activities of various government and private sector bodies. This will be followed by an overview of potential issues that may be encountered with home stockpiling zanamivir or other antivirals for pandemic preparedness around safety and the generation of resistance. Finally, an overview of the proposed studies to support the registration of a Relenza MedKit will be presented.

This Briefing Information was prepared in accordance with FDA's "Guidance for Industry: Advisory Committee Meetings – Preparation and Public Availability of Information Given to Advisory Committee Members", and is considered by GSK to be publicly disclosable information.

1.2. Reason for Development of the Relenza MedKit

In January, 2008, GSK was approached by the Office of BARDA of the US Department of Health and Human Services [US HHS, 2005] who expressed interest in a mechanism by which consumers could receive kits containing Relenza, approved for both the treatment and prophylaxis of influenza, to keep in their homes for use during an influenza pandemic. HHS has previously evaluated emergency "MedKits" through a study designed to provide evidence about the feasibility of placing a cache of antibiotics in individual homes, as an effective measure against release of anthrax. In January 2006, the CDC collaborated with the Missouri Department of Health to evaluate the ability of households to maintain MedKits in homes as directed and to reserve them for emergency use. The study showed that 97% of all study respondents returned the household MedKits upon completion of the study. Of the MedKits returned, all but 34 of the MedKits were intact (more than 99% with no pills missing). An overwhelming majority of study participants appropriately followed instructions regarding storage and reserving the MedKit for use until directed by public officials. FDA requires additional testing on

this MedKit prototype, which is currently under development in BARDA [CDC MedKit Evaluation Study, 2007].

GSK's intent in developing a Relenza MedKit, at the request of HHS, is to provide a safe and effective anti-influenza therapy to be kept in the home for use during an influenza pandemic, prescribed by the consumer's health care provider and used appropriately according to clear guidance and instructions from the necessary public health governing body. Details of the draft components of the Relenza MedKit are provided in Appendix 1.

Although there is no clear precedent for the prescription/provision scenario described here for the Relenza MedKit, there are examples of 'non-traditional' prescription and/or provision of drugs for delayed use. A few of these examples are provided in Appendix 2; GSK personnel have studied the labeling for these products in the interest of applying any apparent learnings to the MedKit.

1.3. Overview of Pandemic Influenza and Current Avian H5N1 Human Infection

Previous pandemics have varied considerably in their pattern. Evidence suggests that the 1957 and 1968 pandemic strains emerged following exchange of genes from human and avian viruses. The 1918 strain, however, is thought to have emerged by stepwise mutation of an avian virus and is estimated to have killed >40 million people worldwide in the course of 1 year. Most deaths occurred in the 15-35 age range. Typically, there was a sudden onset of severe pneumonia, with death from hemorrhagic pneumonia within 48 hours. The 1957 and 1968 pandemics caused milder illness, with fewer deaths (1-2 million worldwide), and mortality occurred typically at the ends of the age spectrum in infants and the elderly, which is characteristic for usual annual flu epidemics.

Recent human cases of highly pathogenic strains of avian influenza (H5N1) have heightened concerns about the imminence of the threat of pandemic influenza. Influenza A H5N1 appears to have similarities with the 1918 strain in terms of its clinical manifestations, the severity of the disease, and the concentration in children and young adults. The first documented outbreak of H5N1 infection in humans occurred in Hong Kong in 1997 and involved 18 cases of which six were fatal. Evidence now strongly indicates that the H5N1 virus has established an unprecedented epizootic presence in Asia and parts of Africa, has become progressively more pathogenic in poultry, and has expanded its mammalian host range. It has been detected in dead wild fowl, isolated from tigers, and experimentally has been shown to infect domestic cats. Additionally, asymptomatic domestic ducks have been shown to excrete H5N1 in its highly pathogenic form providing a reservoir for transmission, and may explain recent human cases that could not be traced back to contact with diseased poultry. As reported by WHO on September 10, 2008, the cumulative number of confirmed human cases of avian influenza since December 26, 2003 reported in Thailand, Viet Nam, Egypt, China, Indonesia and 10 additional countries are 387 cases with 245 fatalities.

1.4. Relenza (Zanamivir) Inhalation Powder

Zanamivir is a potent and highly selective inhibitor of influenza virus neuraminidase

(NA), a surface enzyme involved in the release and spread of virus particles from the cell membrane of epithelial cells in the respiratory tract. An extensive program of clinical studies has been conducted to evaluate the efficacy and safety of zanamivir in both the treatment and prophylaxis of influenza A and B infections.
Zanamivir is currently approved in 109 markets, including the United States and countries of the European Union. In the United States, zanamivir is approved as Relenza (zanamivir) Inhalation Powder and is indicated for:

• **Treatment of influenza** in patients 7 years of age and older who have been symptomatic for no more than 2 days (dose is 10mg twice daily for 5 days).

• **Prophylaxis of influenza** in patients 5 years of age and older (dose is 10mg once daily for 10 – 28 days).

The original New Drug Application (NDA) for the treatment of influenza A and B with Relenza was approved on July 26, 1999 and a supplemental NDA for treatment of pediatric patients was approved on April 26, 2000. A supplemental NDA for the prophylaxis of influenza A and B with Relenza in adult and pediatric patients was approved on March 29, 2006.

Relenza is supplied in a circular foil pack (ROTADISK®) with four blisters each containing 5mg zanamivir and 20mg lactose and is delivered into the lungs by oral inhalation using an inhaler delivery device (Diskhaler®).

1.5. Utility of Antivirals in an Influenza Pandemic

Vaccine strategies are being investigated for the containment of an influenza pandemic. However, because a pandemic situation represents a major antigenic shift, in this situation a vaccine will not be available for at least 6 months leaving most of the population without protective immunity. For this reason, being prepared to administer effective antivirals, both for treatment and for prophylaxis, is thought to be a valuable containment strategy in this scenario.

Although the clinical use of neuraminidase inhibitors has been studied primarily in patients with acute uncomplicated seasonal influenza and this experience cannot be translated directly to human infection with a pandemic influenza strain that might carry a higher pathogenicity, it is still thought that these agents can afford some benefit within the pandemic setting. The prophylactic efficacy of neuraminidase inhibitors has been suggested by the effective prophylaxis of poultry workers during an avian H7N7 poultry outbreak [Koopmans, 2004]. While there are limited available data addressing the efficacy of neuraminidase inhibitors against avian influenza infection in humans, the limited, but well described, case series in the literature does suggest the potential benefit of antiviral treatment in a proportion of patients in whom a rapid decrease in H5N1 viral RNA occurred [Tran, 2004; Oner, 2006; Beigel, 2005]. Further support of efficacy against potential pandemic strains come from *in-vitro* and animal data: as a class, the neuraminidase inhibitors are effective against all neuraminidase subtypes *in vitro*. Data from animal models also suggest efficacy against H5N1, H6N1 and H9N2 viruses [Gubareva, 1998a; Leneva, 2001].

1.6. Antiviral Stockpiling for Pandemic Preparedness

Although the absolute utility of antivirals for the management of pandemic influenza has not been fully interrogated, the stockpiling of neuraminidase inhibitors seems to be a reasonable component of pandemic preparedness. Many governments and private corporations have included zanamivir and oseltamivir within their stockpiling strategy. As part of the US's Pandemic Preparedness plan, the government seeks to stockpile enough antivirals to cover 25% of the US population or approximately 81 million antiviral courses (US DHHS, 2005). Of that 81 million the Federal Government has purchased 50 million (10 million of which was zanamivir) and created subsidized programs to encourage the individual states to purchase the remaining 31 million. As of June 27th, 2008, more than 22 million antiviral units had been purchased by the individual states (US DHHS, 2008).

Many US businesses, especially those with employees deployed oversees, also have stockpiled neuraminidase inhibitors as part of their own pandemic preparedness plans to protect their employees. To date over 300 companies have included antivirals in their pandemic preparedness plans.

1.7. Home Stockpiling of Antivirals

The stockpiling activities of governments and large corporations have prompted discussions on whether private citizens should keep personal stocks of antiviral medications in their homes to protect themselves and their families. Several expert panels and policy making bodies have made recommendations on this issue.

The American College of Physicians [ACP, 2006] stated in its 2006 position paper on Pandemic Influenza, "Stockpiling antiviral medications by individuals will not only contribute to an overall shortage of needed medication, but also may result in the misuse of the medications and result in building resistance to the drugs' effectiveness". The American Academy of Pediatrics (AAP) also discourages personal stockpiles of influenza antivirals. The Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) released a joint statement in 2005: "Neither IDSA nor SHEA support the strategy of personal or family stockpiling of oseltamivir (Tamiflu) to prepare for influenza." and "excessive personal stockpiling would deplete these supplies and make less overall drug available for treatment of priority groups should a pandemic arise in the near future. Personal stockpiling would likely lead to inappropriate use and wastage, as well as foster antiviral drug resistance emergence under some circumstances." Although the manufacturing capacity of antivirals has been increased since the above recommendations were made, such that commitments for the government stockpiles have been met, concerns about inappropriate use and drug resistance still remain. In July 2008, the American Medical Association (AMA), American Association of Family Physicians (AAFP), AAP and IDSA jointly stated "We believe that the available data do not support home stockpiling of antivirals."

GSK shares these concerns and agrees that these are significant issues that must be addressed. At the request of HHS, GSK proposes a development plan for the Relenza MedKit that attempts to address these concerns.

2. OVERVIEW OF SAFETY IN CLINICAL STUDIES

2.1. Safety in Clinical Studies of Zanamivir

Overall, a total of 14,000 subjects have been enrolled into GSK Phase II and III clinical trials for registration and approval of zanamivir, of which over 7,000 subjects have received zanamivir by the inhaled route. Over 1000 were pediatric subjects aged 5 to 12 years, and over 5,000 subjects were high risk or aged ≥ 65 years. A summary of studies in the zanamivir treatment and prophylaxis clinical programs is presented in Table 1 and Table 2.

Table 1 Summary of Clinical Studies in the Zanamivir Treatment Program

	Number of Subjects (Safety Population)				
	Placebo	Zanamivir			Total
	5 days	10mg IH bid 5 days	10mg IH+ 6.4mg IN bid 5 days	10mg IH + 6.4mg IN qid 5 days	
Adult/adolescent					
NAIB3001	228	227			455
NAIA3002	365	412			777
NAIB3002	182	174			356
NAIA/B2005	143	132	141		416
NAIB2007	180	187	182		549
NAIA/B2008	422		419	415	1256
Pediatric					
NAI30009	247	224			471
NAI30010 (index cases)	71	67			138
High Risk and Elderly					
NAI30008	263	261			524
NAI30012	166	191			357

IH = inhaled IN = intranasal bid = twice daily qid = four times daily

Table 2 Summary of Clinical Studies in the Zanamivir Prophylaxis Program

Study	Number of Subjects (Safety Population)				Duration of Prophylaxis
	Placebo	Zanam-ivir	Riman-tadine	Total	
Phase III Studies					
Family/Household					
NAI30010	430	407	N/A	837	10 days
NAI30031	629	661	N/A	1290	10 days
Community					
NAIA3005	554	553	N/A	1107	28 days
NAI30034	1685	1678	N/A	3363	28 days
Nursing Home					
NAIA3003	13	238	231	482	14 days
NAIA3004	252	242	N/A	494	14 days
Phase II Studies					
NAIA2006	15	49	N/A	64	5 days
NAIB2006	32	30	N/A	62	5 days
NAIA/B2009	144	431	N/A	575	5 days

2.1.1. Treatment Studies - Adult and Adolescent Subjects

The safety profile of zanamivir was similar to placebo in the adult/adolescent treatment studies. When data were combined across these six Phase II and Phase III studies, AEs were experienced during treatment by 577/1520 (38%) placebo subjects and 758/2289 (33%) zanamivir subjects. The most commonly reported AEs (≥1.5% incidence) are summarized in Table 3. AEs were generally typical of the signs and symptoms of influenza and occurred with similar frequency in the zanamivir and placebo groups.

In this integrated analysis, one subject in the zanamivir group (1/2289) reported an AE that mapped to the coded term ‘constriction and obstruction of airways’.

Table 3 Summary of the Most Common Adverse Events (During Treatment): Adult and Adolescent Treatment Studies

	Placebo	Zanamivir			
	N=1520 n (%)	10mg bid Inhaled N=1132 n (%)	10mg bid Inhaled + 6.4mg bid Intranasal N=742 n (%)	10mg qid Inhaled + 6.4mg qid Intranasal N=415 n (%)	All Dosing N=2289 n (%)
Any Event	577 (38)	395 (35)	242 (33)	121 (29)	758 (33)
Nasal signs and symptoms	44 (3)	20 (2)	30 (4)	12 (3)	62 (3)
Diarrhea	55 (4)	29 (3)	19 (3)	16 (4)	64 (3)
Nausea	44 (3)	32 (3)	27 (4)	11 (3)	70 (3)
Headaches	40 (3)	20 (2)	26 (4)	6 (1)	52 (2)
Bronchitis	52 (3)	28 (2)	5 (<1)	6 (1)	39 (2)
Cough	42 (3)	27 (2)	13 (2)	2 (<1)	42 (2)
Sinusitis	27 (2)	30 (3)	7 (<1)	5 (1)	42 (2)
Throat and tonsil discomfort	19 (1)	15 (1)	16 (2)	2 (<1)	33 (1)
Vomiting	29 (2)	14 (1)	6 (<1)	4 (<1)	24 (1)
Dizziness	12 (<1)	18 (2)	13 (2)	1 (<1)	32 (1)
Ear, nose and throat infections	25 (2)	17 (2)	9 (1)	5 (1)	31 (1)
Ear, nose and throat hemorrhage[1]	18 (1)	16 (1)	12 (2)	4 (<1)	32 (1)

1. Most of the cases were reported as epistaxis by the investigator.

2.1.2. Treatment Studies – Pediatric Subjects

The safety profile of zanamivir was similar to placebo in the pediatric population. When data from pediatric subjects in Study NAI30009 (pediatric treatment study) and NAI30010 (pediatric index cases from family prophylaxis study) were combined, AEs were experienced during treatment by 84/318 (26%) placebo subjects and 62/291 (21%) zanamivir subjects. The most commonly reported AEs were ear, nose and throat infections (5% both groups), vomiting (3% placebo subjects, 2% zanamivir subjects) and diarrhea (2% both groups).

In this analysis, no subjects reported an AE that mapped to the coded term ‘constriction and obstruction of airways’.

2.1.3. Treatment Studies – High-Risk Subjects

High risk subjects were defined as: subjects 65 years of age and above; subjects with a cardiovascular, respiratory, metabolic or endocrine condition; or subjects who were immunocompromised. An integrated analysis of safety data from all high-risk subjects in the adult/adolescent treatment studies and Study NAI30008 (treatment study in

asthma/COPD), but with the exception of Study NAI30012 (treatment study in the elderly, which was analyzed separately), included a total of 982 subjects.

In this integrated analysis, the proportion of subjects who reported an AE during treatment was similar in the placebo group (202/480 subjects, 42%) compared with the zanamivir group (188/502 subjects, 37%). The most commonly reported AEs were typical of the signs and symptoms of influenza and/or the underlying medical conditions of the high-risk subjects, and occurred with similar frequency in zanamivir and placebo groups. Similar numbers of subjects in both zanamivir and placebo groups (49 subjects, 10% in both groups) reported a drug-related AE during treatment.

High-Risk Elderly: A total of 274 subjects aged ≥ 65 years received zanamivir for the treatment of influenza in clinical studies. The majority of these subjects were enrolled in Study NAI30012, in which 191 subjects received zanamivir and 167 received placebo. In this study, the incidence of AEs was similar in the placebo (30%) and zanamivir (35%) groups. The most frequently reported AE was bronchitis (11% in the placebo group and 5% in the zanamivir group). The safety profile of zanamivir in elderly subjects was not different from that of placebo and no specific safety issues were identified. One subject, who was in the placebo group, reported an AE which was coded under the AE term 'Airways constriction and obstruction'.

High-Risk Respiratory: An integrated analysis of safety data from all high-risk subjects with a respiratory condition in the adult/adolescent treatment studies and Study NAI30008 (treatment study in asthma/COPD), but with the exception of Study NAI30012 (treatment study in the elderly, which was analyzed separately), included a total of 812 subjects. The frequency of AEs in this sub-group was very similar to that reported for the High-Risk Population as a whole. In 812 subjects in this integrated analysis, AEs were reported during treatment by 44% of placebo and 38% of zanamivir recipients. Asthma and bronchitis were the most frequently reported AEs during treatment: asthma was reported in 10% of placebo and 7% of zanamivir recipients, and bronchitis was reported in 8% of placebo and 3% of zanamivir recipients. Events of bronchospasm were reported only in Study NAI30008 (treatment study in asthma/COPD): four subjects (2%) in the placebo group reported an AE which was coded under the AE term 'Airways constriction and obstruction'; there were no reports of AEs specifically described as bronchospasm in subjects who received zanamivir.

Pulmonary Function in Study NAI30008 – Treatment Study in Patients with Asthma/COPD: Pulmonary function was assessed in Study NAI30008, a treatment study in adult/adolescent patients with asthma and/or COPD. Peak expiratory flow rate (PEFR) was measured twice daily and also during clinic visits at baseline, Day 6 and Day 28. Forced expiratory volume in one second (FEV_1) was measured at clinic visits only. Tests were done before use of a short acting bronchodilator.

There were small but statistically significant increases in both the morning PEFR and evening mean PEFR over Days 1-5 in the zanamivir group vs. placebo group (morning: 12.9L/min, 95% CI 3.0, 22.9, p=0.011; evening: 13.1 L/min, 95% CI 3.6, 22.7, p=0.007). Small increases were also seen over Days 1-14 and 1-28, although the difference between the two treatments did not reach statistical significance.

There was no statistically significant difference between treatment groups in mean clinic FEV_1 or mean PEFR on Days 6 or 28.

Decreases in clinic FEV_1 >20% compared with baseline were seen for 22 (9%) placebo subjects and 24 (10%) zanamivir subjects at Day 6, and for 15 (7%) placebo subjects and 17 (7%) zanamivir subjects at Day 28. Decreases in clinic PEFR >20% compared with baseline were seen for 9 (4%) placebo subjects and 10 (4%) zanamivir subjects at Day 6, and for 5 (2%) subjects in both treatment groups at Day 28.

Overall, was no evidence of any deleterious effect of inhaled zanamivir compared with placebo on pulmonary function. There was evidence of greater improvements in PEFR following the start of therapy in the zanamivir group compared with the placebo group.

2.1.4. Prophylaxis Studies

The frequency and nature of AEs reported during prophylaxis in the six Phase III studies were similar between the placebo and zanamivir groups. During prophylaxis, the frequency of AEs in the placebo, zanamivir and rimantidine treatment arms was between 51 and 58%. The most commonly reported AEs (≥1.5% incidence) during prophylaxis are presented in Table 4. Many of these are typical of the signs and symptoms of influenza and other viral respiratory infections.

In this integrated analysis, adverse events mapping to the coded term 'airways constriction and obstruction' were reported by seven subjects, four in the placebo group (4/ 3550, <1%) and three in the zanamivir group (3/3541, <1%).

Table 4 Most Common Adverse Events (During Prophylaxis): Phase III Prophylaxis Studies

Adverse Event	NAI30010, NAI30031, NAIA3005, NAI30034, and NAIA3004 combined		NAIA3003	
	Placebo N=3550 n (%)	Zanamivir N=3541 n (%)	Rimantadine N=231 n (%)	Zanamivir N=238 n (%)
Any Event	1899 (53)	1797 (51)	128 (55)	137 (58)
Headaches	743 (21)	696 (20)	15 (6)	25 (11)
Throat and tonsil discomfort and pain	551 (16)	517 (15)	21 (9)	18 (8)
Cough	532 (15)	478 (13)	39 (17)	38 (16)
Nasal signs and symptoms	438 (12)	427 (12)	31 (13)	30 (13)
Temperature regulation disturbances	282 (8)	261 (7)	10 (4)	10 (4)
Malaise and fatigue	242 (7)	241 (7)	19 (8)	22 (9)
Viral respiratory infections	283 (8)	217 (6)	0	1 (<1)
Muscle pain	213 (6)	217 (6)	6 (3)	5 (2)
Musculoskeletal pain	148 (4)	147 (4)	8 (3)	19 (8)
Diarrhea	63 (2)	64 (2)	9 (4)	13 (5)
Gastrointestinal signs and symptoms	15 (<1)	13 (<1)	14 (6)	14 (6)
Dizziness	20 (<1)	21 (<1)	2 (<1)	11 (5)
Vocal cord disorders	10 (<1)	9 (<1)	9 (4)	13 (5)
Constipation	11 (<1)	5 (<1)	8 (3)	13 (5)

2.1.5. Review of Neuropsychiatric Events in Zanamivir Clinical Studies

A review of neuropsychiatric adverse events was performed for data in all GSK Phase II and III clinical studies of zanamivir used in the registration and approval of zanamivir (14,810 subjects enrolled, 8033 treated with zanamivir) and studies conducted by GSK Japan (1049 subjects, 687 treated with zanamivir). FDA specified adverse event terms in the nervous system, psychiatry and injury, poisoning and procedural complications body systems were used to select the events of interest for this review. Overall 383/14,810 (2.6 %) subjects reported a total of 420 events. In both placebo controlled studies and rimantadine controlled studies, the frequencies and nature of events was similar between the zanamivir and the control group within each type of control setting. In the placebo controlled studies, the most common events were in the High Level Group Term (HLGT) of 'Sleep disorders and disturbances', while in the rimantadine controlled studies the most common events were in the HGLT of 'Injuries'. There was no evidence of a causal association between zanamivir use and suicide or parasuicide. This review did not show an increased incidence of neuropsychiatric events in subjects who received zanamivir compared with those who received placebo, or a comparator drug.

2.1.6. Summary of Safety in Clinical Studies

Overall, a total of 14,000 subjects have been enrolled into Phase II and III clinical trials of zanamivir, of which over 7,000 subjects have received zanamivir by the inhaled route.

Safety data from both treatment and prophylaxis studies indicate that zanamivir has an adverse event profile similar to placebo. No differences were observed between treatment groups in the studies involving children, the elderly or high-risk subjects. There were no differences in the incidences of respiratory or neuropsychiatric events between zanamivir and placebo.

2.2. Safety Relating to Lactose Vehicle in the Inhaled Dry Powder Formulations

All safety data from the zanamivir clinical studies reflects administration of zanamivir and matching placebo by oral inhalation via ROTADISK/DISKHALER. Therefore, the extent to which inhalation of the dry powder vehicle itself may contribute to adverse events cannot be discerned from the zanamivir clinical studies. To evaluate the potential association of inhalation of lactose dry powder in the ROTADISK and lower respiratory adverse events, additional analyses of data from GSK sponsored studies in the respiratory therapeutic area were performed. This approach was suggested by regulatory reviewers, and was submitted as part of the supplemental NDA for the zanamivir prophylaxis indication in 2005.

Studies from the GSK US Asthma Database were selected for the purpose of comparing relevant lower respiratory AEs since there is the potential to assess the safety of placebo as a dry powder (lactose) versus an alternative formulation (chlorofluorocarbon (CFC) aerosol given by metered dose inhaler [MDI]) in these studies. The placebo drug products used in these GSK-sponsored asthma studies were the DISKUS™ (13mg lactose fill weight in each inhalation blister) and the ROTADISK (25mg lactose fill weight in each inhalation blister). The fill weight of lactose in the Relenza Rotadisk is 25mg.

2.2.1. Selection of Studies from the GSK US Asthma Database

At the time of the analysis, there were 135 studies in the US Asthma Database including studies of salmeterol (SEREVENT™), fluticasone propionate FLOVENT™/FLIXOTIDE™), and fluticasone propionate/ salmeterol combination (ADVAIR™/SERETIDE™). Studies were selected for these additional analyses based on inclusion of a relevant placebo group and similarity in design to the zanamivir clinical studies. The key selection criteria were as follows:

- a placebo treatment arm with BID dosing via a single inhalation device (i.e., MDI or dry powder inhaler),
- parallel group design,
- a 12-week treatment period (a uniform and classically accepted duration of treatment in pivotal clinical studies of patients with asthma), and
- an adolescent/adult population with asthma.

A total of sixteen clinical studies were identified:

- nine studies with informative clinical safety data on a placebo MDI; these studies of 1,018 patients form the "placebo aerosol" group in pooled safety analyses presented below.

- seven studies with informative clinical safety data on a placebo dry powder inhaler were identified; these studies of 530 patients form the "placebo dry powder" group in pooled safety analyses presented below.

While these two pools of prospective clinical trials provide an opportunity to compare the frequencies of clinical adverse events for inhaled lactose-containing dry powder placebo versus inhaled metered-dose aerosols, limitations were also noted: the comparisons were between-study and not within-study; and unlike clinical studies with zanamivir the AE term "asthma" was regarded as exempt from reporting as an adverse event, unless it met the definition of a serious adverse event (since asthma was the disease under study).

A stepwise approach was taken. The incidence of the following AEs were examined for each placebo group:

- Lower respiratory AEs of interest based on predefined adverse event coded terms
- 'Bronchospasm-like' AEs based on review of investigator text from the above coded terms
- AEs that map to the coded term 'airways constriction and obstruction'
- AEs containing the specific term 'bronchospasm'.

2.2.2. Lower Respiratory Adverse Events of Interest

First, coded adverse event terms were reviewed to prospectively determine those terms that may include an event related to bronchospasm or a 'bronchospasm-like' decline in lung function. Most of these events were contained in the "lower respiratory" body system; there was also one term ("chest symptoms") identified from the "non-site specific" body system that could possibly contain an event related to bronchospasm. Using this approach, all adverse events that mapped to the prespecified coded terms were captured and summarized as "lower respiratory adverse events of interest". Lower respiratory adverse events of interest consisted of the following coded terms: asthma, breathing disorders, bronchitis, chest sounds, airway constriction and obstruction, lower respiratory signs and symptoms, chronic obstructive airways disease, lung disorders, allergic lower respiratory disorders, lower respiratory failure, chest symptoms.

The frequency of 'lower respiratory AEs of interest' for each placebo group (dry powder versus MDI) is summarized in Table 5. As shown in Table 5, 14 of 530 patients (2.6%) using placebo dry powder compared with 67 of 1,018 subjects (6.6%) using placebo aerosol had one or more lower respiratory adverse events of interest.

Table 5 Frequency of Lower Respiratory AEs of Interest by Body System in Previous Studies of Inhaled Respiratory Medications (ITT Population)

	Placebo Dry Powder (N=530)	Placebo Aerosol (N=1018)
No. (%) Subjects with at least one AE	14 (3%)	67 (7%)
Lower Respiratory, any event	6 (1%)	50 (5%)
Bronchitis	3 (<1%)	23 (2%)
Acute bronchitis	1 (<1%)	9 (<1%)
Status asthmaticus	0	6 (<1%)
Asthmatic bronchitis	1 (<1%)	3 (<1%)
Exacerbation of asthma	1 (<1%)	1 (<1%)
Shortness of breath	0	2 (<1%)
Wheeze	0	2 (<1%)
Breathing disorder	0	1 (<1%)
Choking sensation	0	1 (<1%)
Exacerbation of dyspnea	0	1 (<1%)
Exacerbation of wheezing	0	1 (<1%)
Respiratory arrest	0	1 (<1%)
Rhonchi	0	1 (<1%)
Respiratory[1], any event	8 (2%)	9 (<1%)
Bronchitis	4 (<1%)	4 (<1%)
Chest tightness	2 (<1%)	1 (<1%)
Wheezing	1 (<1%)	2 (<1%)
Asthma	2 (<1%)	0
Dyspnea	0	2 (<1%)
Non-Site Specific, any event	0	8 (<1%)
Chest tightness	0	8 (<1%)
Ear Nose & Throat, any event	0	1 (<1%)
Tightness of throat	0	1 (<1%)

1. This body system represents AEs coded under the DISS coding dictionary. Other AEs were coded under the MIDAS dictionary.

2.2.3. 'Bronchospasm-Like' Adverse Events

Following the above review of lower respiratory AEs of interest, a further, more in depth, review was performed in order to focus on specific adverse events that could in any way be considered indicative of bronchospasm. In this analysis, a case-by-case review was conducted of the investigator text for each adverse event identified as a 'lower respiratory AE of interest'. These were designated 'bronchospasm-like' AEs.

The frequency of 'bronchospasm-like' AEs based on adverse event investigator text review for each placebo group (dry powder versus MDI) is provided in Table 6.

Fewer 'bronchospasm-like' AEs were reported in the placebo dry powder group (also the vehicle for zanamivir) than with the placebo aerosol group.

Table 6 Frequency of 'Bronchospasm-Like' AEs by Body System in Previous Studies of Inhaled Respiratory Medications (ITT Population)

	Placebo Dry Powder (N=530)	Placebo Aerosol (N=1018)
No. (%) Subjects with at least one AE	6 (1%)	31 (3%)
Lower Respiratory, any event	2 (<1%)	18 (2%)
Status asthmaticus	0	6 (<1%)
Asthmatic bronchitis	1 (<1%)	3 (<1%)
Exacerbation of asthma	1 (<1%)	1 (<1%)
Shortness of breath	0	2 (<1%)
Wheeze	0	2 (<1%)
Breathing disorder	0	1 (<1%)
Exacerbation of dyspnea	0	1 (<1%)
Exacerbation of wheezing	0	1 (<1%)
Respiratory arrest	0	1 (<1%)
Rhonchi	0	1 (<1%)
Respiratory[1], any event	4 (<1%)	5 (<1%)
Chest tightness	2 (<1%)	1 (<1%)
Wheezing	1 (<1%)	2 (<1%)
Asthma	2 (<1%)	0
Dyspnea	0	2 (<1%)
Non-Site Specific, any event	0	8 (<1%)
Chest tightness	0	8 (<1%)
Ear Nose & Throat, any event	0	1 (<1%)
Tightness of throat	0	1 (<1%)

1. This body system represents AEs coded under the DISS coding dictionary. . Other AEs were coded under the MIDAS dictionary.

2.2.4. Adverse Events coded under the term 'Airways Constriction and Obstruction'

After identifying 'lower respiratory AEs of interest' and 'bronchospasm-like' AEs as reported above, the next step was to highlight adverse events that mapped only to the coded term of 'airways constriction and obstruction' in order to provide more stringent identification of subjects likely to have experienced bronchospasm. No adverse event mapped to the coded term of 'airways constriction and obstruction'.

2.2.5. Adverse Events containing the specific term 'Bronchospasm'

The last step in this series of analyses was to capture only those adverse events with investigator text containing the specific term 'bronchospasm'. There was no adverse event with investigator text that included the term 'bronchospasm'.

2.2.6. Summary of Findings from Analysis of Lactose Data in Inhaled Medication

Although these formulations were not directly compared within the same studies, these results from a relatively large group of subjects inhaling "placebo dry powder" (i.e., lactose) do not show any signal of a greater frequency of lower respiratory adverse events than "placebo aerosol" (not containing lactose).

3. OVERVIEW OF ZANAMIVIR SPONTANEOUS EVENTS SAFETY DATABASE

From March 1999, date of zanamivir first launch, through to 31 July 2008, a total of 1408 spontaneous adverse event reports (cases) involving subjects who had received zanamivir for either treatment or prophylaxis of influenza were received world wide by Global Clinical Safety and Pharmacovigilance (GCSP) of GSK Research and Development Ltd (GSK Research & Development [R&D]). Characteristics of the 1408 spontaneous reports present on the database on the 31 July 2008 are:

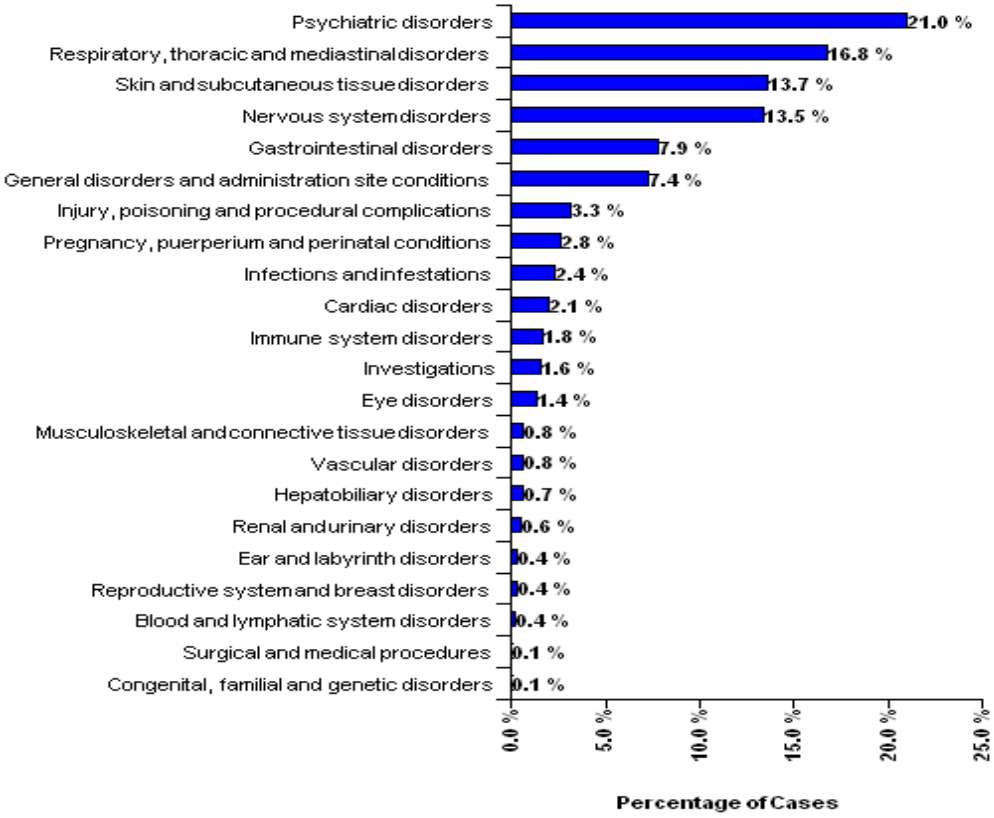
- The majority of cases originated in Japan (52.5%), USA (16.6%), Canada (9.2%) and Germany (6.5%).
- (19.3%) were reported by consumers (not medically confirmed).
- (30.5%) were assessed as ‘serious’ (FDA criteria) and/or were considered medically serious by GSK.

3.1. Patient Exposure

Based on IMS (Intercontinental Medical Statistics) Health data, postmarketing exposure from launch to June 2008 is estimated to be 7.6 million treatment courses. This has been calculated using available sales volumes data concerning numbers of units sold, where one unit is assumed to equate to one Diskhaler with 5 days supply of zanamivir. Note that this estimate does not include product purchased for government stockpiling purposes in anticipation of an influenza pandemic.

3.2. Spontaneous Cases (n=1408)

Distribution of spontaneously reported cases by System Organ Class (SOC)



The largest proportion of cases thus involved a primary event in the psychiatric disorders body system, with the most commonly reported events being: hallucinations, delirium, restlessness and agitation. Notably, all these reports were received from Japan and the majority of these reports (67%) were received in 2007. The respiratory, thoracic, mediastinal disorders body system contained the second largest proportion of cases with the most medically significant primary events including dyspnea, bronchospasm wheezing and asthma.

Over the last few years, neuropsychiatric disorders and events relating to bronchospasm have been the main areas of focus related to zanamivir safety, as reflected by the high proportion of zanamivir cases in the psychiatric and respiratory disorder body systems. An updated overview of these areas of interest is therefore presented here.

3.2.1. Overview of Neuropsychiatric Disorders with Zanamivir

3.2.1.1. Recent label changes related to neuropsychiatric disorders

A comprehensive review of neuropsychiatric events reported with zanamivir was undertaken in October 2007 at the request of the FDA and a summary can be found in Appendix 3.

The main focus of the analysis was a cluster of 145 adverse neuropsychiatric events reported in children and adolescents treated with zanamivir. These cases were received from Japan in the spring of 2007, and occurred at the peak of the Japanese influenza season. The events most frequently reported were: abnormal behavior, hallucination, agitation, delirium, headache, restlessness, speech disorder, dizziness, crying and fear. They followed the public release of a high level alert by the Japanese Ministry of Health, Labor and Welfare in February 2007 detailing abnormal / self harm behaviors observed in Japanese adolescents with influenza infection exposed to oseltamivir.

The assessment of spontaneous reports of psychiatric or neuropsychiatric events is complex, and especially so in children. Therefore, information from additional sources (pre-clinical, pharmacokinetic, clinical trials, epidemiology and literature) was included in the company's assessment of this issue in addition to adverse event reports from the GSK global safety database.

The analysis of all available information did not provide convincing evidence of a causal association of accidents, neurological or psychiatric events, including convulsions, loss of consciousness, suicidal ideation, depression or self-harm behavior with zanamivir.

Nonetheless, as a precaution, the following statement was added to the US Prescribing Information (USPI) for zanamivir (Appendix 4):

> **Warnings and Precautions**
>
> Influenza can be associated with a variety of neurologic and behavioral symptoms which can include events such as seizures, hallucinations, delirium, and abnormal behavior, in some cases resulting in fatal outcomes. These events may occur in the setting of encephalitis or encephalopathy but can occur without obvious severe disease.
>
> There have been postmarketing reports (mostly from Japan) of delirium and abnormal behavior leading to injury in patients with influenza who were receiving neuraminidase inhibitors, including RELENZA. Because these events were reported voluntarily during clinical practice, estimates of frequency cannot be made, but they appear to be uncommon based on usage data for RELENZA. These events were reported primarily among pediatric patients and often had an abrupt onset and rapid resolution. The contribution of RELENZA to these events has not been established. Patients with influenza should be closely monitored for signs of abnormal behavior. If neuropsychiatric symptoms occur, the risks and benefits of continuing treatment should be evaluated for each patient.

In addition, the following relevant statements are included in the **Adverse Reactions - Postmarketing Experience** section of the USPI (Appendix 4)

> *Psychiatric:* Delirium, including symptoms such as altered level of consciousness, confusion, abnormal behavior, delusions, hallucinations, agitation, anxiety, nightmares
>
> *Neurologic:* Seizures

3.2.1.2. Update of review of neuropsychiatric events with zanamivir

GSK has conducted a further analysis of adverse neuropsychiatric events received with zanamivir, considering relevant individual adverse event reports received since the review described above. The GSK worldwide safety database was searched using the following criteria:

- **Data lock points:** 01 Jul 2007 to 31 Jul 2008
- **Report types:** All spontaneous reports, post-marketing surveillance reports, and unblinded serious cases from clinical trials.
- **Suspect drug:** Zanamivir
- **MedDRA search terms:** All adverse event terms specified by FDA in correspondence from May 2nd and Sept 20th 2007. The selected terms fall within three Body System Organ Classes (SOC); Injury, Poisoning and Procedural Complications, Nervous System Disorders, Psychiatric disorders

The results of the analysis can be summarized as follows:

- A total of 194 relevant reports were identified of which 187 were received during the most recent Northern hemisphere influenza season (Oct-2007 to Jun-2008).
- All but one of the reports was from Japan
- Most cases (>90%) involved children and adolescents.
- Most events were consistent with the natural course of influenza infection, often describing abnormal/delirious behavior in patients with documented fever. Events were generally transient with the majority described as resolved or improved at the time of the report.

Although a causal association with zanamivir could not be ruled out in a small number of cases, there was no evidence of any consistent pattern of events. In particular, there was no convincing evidence of a causal association between zanamivir and convulsions, loss of consciousness, suicidal ideation, depression or self harm.

These cases are therefore considered to be adequately described by the current USPI statements (Appendix 4) and no change to the zanamivir label is warranted.

3.2.2. Overview of Bronchospasm and Related Events with Zanamivir

3.2.2.1. Current zanamivir labeling regarding bronchospasm and related events

It is difficult to assess the causal association between zanamivir and respiratory events for a number of reasons. Firstly, influenza itself can cause hyper-reactivity of the airways and, secondly, influenza is associated with exacerbations of asthma, COPD and emphysema. These effects are also often caused by secondary bacterial infections. A

number of reports of respiratory events received for zanamivir contain insufficient information to be adequately evaluated, in particular those cases which lack information on temporal relationship and medical history. However, there are cases in which the events occurred a short time after administration of zanamivir and so a causal association cannot be excluded.

Zanamivir labeling was therefore updated regarding respiratory events in 2000 following a detailed evaluation of spontaneous reports of respiratory events and subsequent discussions with the US and European regulatory authorities. In particular, bronchospasm and dyspnea were highlighted by this review and were added as undesirable effects in the USPI for zanamivir (Appendix 4). In addition, information concerning the risk of occurrence of bronchospasm and some prevention measures was incorporated into the USPI.

Relevant statements from the USPI are as follows:

> **DOSAGE AND ADMINISTRATION**
>
> **Dosing Considerations**
>
> Patients scheduled to use an inhaled bronchodilator at the same time as RELENZA should use their bronchodilator before taking RELENZA
>
> **WARNINGS AND PRECAUTIONS**
>
> **Bronchospasm**
>
> RELENZA is not recommended for treatment or prophylaxis of influenza in individuals with underlying airways disease (such as asthma or chronic obstructive pulmonary disease).
>
> Serious cases of bronchospasm, including fatalities, have been reported during treatment with RELENZA in patients with and without underlying airways disease. Many of these cases were reported during postmarketing and causality was difficult to assess.
>
> RELENZA should be discontinued in any patient who develops bronchospasm or decline in respiratory function; immediate treatment and hospitalization may be required.
>
> Some patients without prior pulmonary disease may also have respiratory abnormalities from acute respiratory infection that could resemble adverse drug reactions or increase patient vulnerability to adverse drug reactions.
>
> Bronchospasm was documented following administration of zanamivir in 1 of 13 patients with mild or moderate asthma (but without acute influenza like illness) in a Phase I study. In a Phase III study in patients with acute influenza like illness superimposed on underlying asthma or chronic obstructive pulmonary disease,

10% (24 of 244) of patients on zanamivir and 9% (22 of 237) on placebo experienced a greater than 20% decline in FEV1 following treatment for 5 days.

ADVERSE REACTIONS

Post-marketing Experience

Respiratory: Bronchospasm, dyspnea

An updated analysis of bronchospasm, covering individual adverse event reports received since the review in 2000 was conducted in 2005. The cases reviewed were consistent with previous reports of bronchospasm in patients with zanamivir.

3.2.2.2. Updated review of bronchospasm with zanamivir

GSK has conducted a further review of bronchospasm with zanamivir, considering all relevant individual case reports received since the data cut off for the previous review. The search strategy was as follows:

- **Data lock points:** 01 Aug 2005 to 31 Jul 2008
- **Report types:** All spontaneous reports, post-marketing surveillance reports, and unblinded serious cases from clinical trials.
- **Suspect drug:** Zanamivir
- **MedDRA search terms (preferred terms)**

  Acute respiratory distress syndrome
  Asthma
  Bronchial obstruction
  Bronchospasm
  Chronic obstructive pulmonary disease
  Peak expiratory flow rate decreased
  Respiratory distress
  Status asthmaticus
  Wheezing

A total of two reports were identified, both were spontaneous reports from Japan:

- In the first a patient had a syncope-like event immediately following inhalation of a zanamivir demonstration kit. Although the events were initially described as anaphylactic shock, later information stated there were no anaphylactic symptoms. The only respiratory symptom reported was “weak breathing”. The reporter stated that “inhalation of lactose might have triggered nonspecific vagal reflex, and caused transient decrease of BP”.
- The second case involved a patient who received zanamivir for 5 days for influenza. The day after zanamivir treatment was completed the patient had

wheezing, chest discomfort/heaviness, cough and throat discomfort. The events resolved gradually over the following three weeks.

These cases do not represent new safety information regarding bronchospasm with zanamivir and no amendments to USPI (Appendix 4) are required.

3.2.3. Overview of Other Safety Issues with Zanamivir

Since first marketing, amendments have been made to the zanamivir prescribing information as and when new safety information has been identified. In addition to the respiratory and neuropsychiatric events discussed above, the following statements have also been added to the USPI (Appendix 4) on the basis of post-marketing data:

Adverse Reactions

Post- Marketing data

General:
Very rare: Allergic-type reaction, including facial and oropharyngeal edema

Skin
Very rare: rash, urticaria

3.2.4. Summary of Spontaneous Adverse Events

The safety profile of zanamivir is under regular review, and the prescribing information for the inhaled formulation has been and will continue to be updated as new or changing information is identified. Respiratory and neuropsychiatric events have been highlighted as the main areas of interest with zanamivir over recent years and a number of statements around these events have been included in the USPI for zanamivir (Appendix 4). Reviews of these areas have been updated and no new information has been identified.

No new safety issues are apparent from this review of post-marketing safety data and the safety profile of zanamivir is considered to be adequately described in the current USPI.

4. OVERVIEW OF VIRAL RESISTANCE

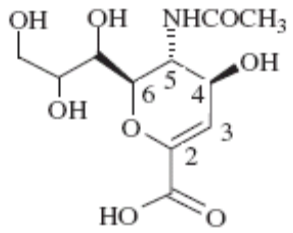
4.1. Natural Barriers to Resistance

Influenza is a respiratory infection caused by influenza A and B viruses, and generally is a self-limiting disease in man with virus cleared within 6 days due to local immune responses. Mortality associated with influenza occurs most frequently in the elderly or in those with underlying disease, and is highest during pandemics when the influenza strains may be more virulent and natural immunity is lowest. Influenza viruses replicate rapidly

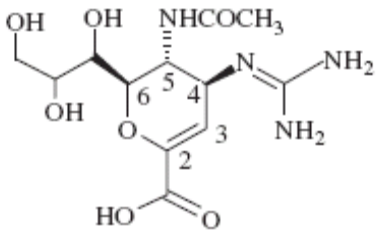
within the respiratory tract over the first 24-48 hours of infection causing severe damage to the ciliated respiratory epithelium, and which result in some of the typical signs and symptoms of influenza [Boivin, 2000]. The risks of development of resistance due to poor compliance or less control over usage should be much lower with a self-limiting disease with treatment for just 5 days compared with prolonged therapy of chronic infections such as HIV. In immunocompromised patients where replication continues for longer periods, the risk of resistance may be greater, but fitness of resistant isolates may be compromised [Gubareva, 1998b].

Zanamivir inhibits influenza replication and was designed to target the highly conserved active site of the influenza neuraminidase which is essential for release and spread of virus in the respiratory tract. All NA inhibitors (NAIs) are based on the structure of 2, 3-dehydro-2-deoxy-N-acetyl neuraminic acid (DANA), a transition state analogue of sialic acid, the natural substrate, generated during catalysis (Figure 1). Zanamivir was synthesized by substituting the O-4 hydroxyl group with a guanidinium group. Zanamivir was designed as a close mimic of the natural substrate and binds in the NA active site in a similar way to that of DANA which appears to limit the potential for resistance development to zanamivir [Varghese, 1998; Smith, 2002; Collins, 2008].

Figure 1 Chemical structures of DANA and Zanamivir



Neu5Ac2en (DANA)



Zanamivir (GG167, Relenza)

4.2. *In vitro* Selection of Resistance Mutations to Zanamivir

In vitro selection of zanamivir resistance mutations has been carried out in several studies by passaging influenza virus in the presence of increasing concentrations of zanamivir and the NA mutations selected are summarized in Table 7 [Barnett, 1999; Baz, 2007; Blick, 1995; Blick, 1998; Gubareva, 1996a; Gubareva, 1996b; Gubareva, 1997; Mckimm-Breschkin, 1996; Mckimm-Breschkin, 1998; Staschke, 1995]. Mutants with mutations in only the HA are excluded from the table. The selection of zanamivir resistance mutations is relatively difficult and requires several passages to high compound concentrations, compared with just one or two passes with amantadine. The first mutations observed *in vitro* during zanamivir passage are HA mutations which can produce resistance to zanamivir due to reduced dependence on neuraminidase in cell culture, but which retain susceptibility *in vivo* (Barnet *et al.* 1999). In addition, three different mutations have been observed in the neuraminidase active site at residue E119, which interacts with the guanidino side-chain of zanamivir. These mutations are E119G/A/D in influenza A (H1N9), A (H4N2) and influenza B strains. The only other

active site mutations observed in an avian A(H4N2) strain was R292K, and one passage study with zanamivir with an A(H1N1) strain produced a large deletion within NA.

Further studies have been undertaken *in vitro* using reverse genetics to reconstruct zanamivir mutations into a known N2 background. This revealed that only two known zanamivir mutations when introduced into the A/N2 NA, E119D and R292K, conferred resistance to zanamivir with a Fold Change (FC) of 32 and 2.5 respectively [Zürcher, 2006]. However, three further known zanamivir mutations when introduced into N2 at E119G, E119A and R152K were unstable suggesting that they have compromised virus viability. Furthermore, some resistant variants (R152K, R292K) selected for by neuraminidase inhibitors in the clinic have resulted in reduced neuraminidase enzyme stability or function and reduced infectivity and pathogenicity *in vivo* in the mouse or ferret models [Gubareva, 1998a; Herlocher, 2002]. This suggests that some variants would have extremely limited chances of transmission in man and therefore should not compromise treatment of influenza epidemics.

Table 7 NA resistance Mutations selected *In vitro* by Zanamivir

Type/Sub-type	NA Mutation N2 numbering	HA Mutation H3 numbering	Fold Change to Zanamivir	References
A/H1N9 (human /avian recombinant)	E119G E119G	None S186F	>250	Blick 1995, Blick 1998
A/H1N9 (human/ avian recombinant)	E119G	None	>200	Staschke 1995
B/(human)	E119G E119G	N145S N150S	>200	Staschke 1995
A/H4N2 (Avian)	E119G	None	700	Gubareva 1996a & Gubareva 1996b, Gubareva 1997
A/H4N2 (Avian)	E119A/R249K*	G75E	600	
A/H4N2 (Avian)	E119D	None	2500	
A/H4N2 (avian)	R292K	Y234L/T267K/ D304N/K68R	10	
B/(Human)	E119G	L226Q, V93A	>2000	Barnett 1999
A/H1N1 (Human recombinant)	Deletion 92-362	A200T	NA activity too low for assay	Baz 2007

*NA mutations recorded outside the NA active site, probably due to natural variation

4.3. Zanamivir Resistance in Clinical Studies and Clinical Practice

In clinical trials in more than 14,000 immmunocompetent subjects, during treatment or prophylaxis with zanamivir, no development of resistance to zanamivir has been observed. In addition there have been a total of 7,488,000 treatment doses of zanamivir prescribed worldwide without any recorded case of resistance. Only one influenza virus (influenza B) with decreased sensitivity to zanamivir has been isolated [Gubareva, 1998b). This was isolated from an immunocompromised patient following prolonged treatment with an investigational nebulized formulation of zanamivir, in which a novel mutation (R152K) not previously seen *in vitro* (Table 8) was identified after 15 days treatment.

4.4. Cross Resistance Analysis of NAI Resistant Clinical Isolates

Zanamivir and oseltamivir target the same region, the active site of the NA molecule, and therefore it may be expected that both drugs would show high levels of cross-resistance. However, because the two molecules bind in different ways within the active site, not all mutations show cross-resistance or the levels of resistance observed are different. These differences could be important in the clinic for use of the two drugs if resistance should become a problem. In particular, zanamivir appears to show a lower potential for resistance development possibly because it more closely mimics the structure of the natural substrate [Smith, 2002, Collins 2008]. A total of 11 NA residues within the enzyme active site region have been linked with NAI resistance in the clinic to date and are listed in Table 8. Some of the mutations at catalytic residues show some cross-resistance, but have severely compromised enzyme function and show low potential for virus transmission, whereas other framework (structural) mutations have less effect on enzyme function and may have greater potential for transmission in man.

Four resistant mutations (H274Y, E119V, N294S and I221T) selected by oseltamivir in the clinic are sensitive to zanamivir. The mutation H274Y in A/H1N1 viruses confers a shift in susceptibility to oseltamivir of 900 fold while retaining full sensitivity to zanamivir. In the past 12 months, the H274Y mutation has been identified in A (H1N1) seasonal influenza isolates worldwide in subjects not treated with neuraminidase inhibitors [Lackenby, 2008]. Overall, an incidence of 16% was reported in the Northern Hemisphere 2007-2008 influenza season, with the highest in Norway (67%) [WHO, 2008]. These findings support recommendations from HHS to include both oseltamivir and zanamivir within stockpiling programs.

Table 8 NAI-Resistance Mutations Observed in the Clinic after treatment with NAIs

Mutant	Sub-Type	Selected By	Resistance (R) Oseltamivir (Fold-Shift)	Resistance (R) or Sensitivity (S) Zanamivir (Fold-Shift)	Potential for Transmission
R292K	A/N2	Oseltamivir	R (>8000)	R (4-25)	Unlikely
R152K	B	Zanamivir (Immunocompromised)	R (12-76)	R (9-150)	Unlikely
H274Y[1]	A/N1	Oseltamivir	R (900)	S	Possible
E119V	A/N2	Oseltamivir	R (>50)	S	Possible
D198N	B	Oseltamivir	R (9)	R (9)	Not known
N294S	A/N2	Oseltamivir	R(300)	S	Not known
N294S[2]	A/N1	Oseltamivir	R (12-15)	S (4.8)	Not Known
G402S	B	Oseltamivir	R (3.9*)	R (7)	Not Known
246-248 deletion	N2	Oseltamivir (immunocompromised)	R (20)	R (9)	Not Known
A117V	N1	Oseltamivir (immunocompromised)	R (15)	R(13.8)	Not Known
I221T	B	Oseltamivir (Immunocompromised)	R (13)	S (2.1)	Not Known

References:- Le, 2005; Mishin, 2005; Hatakeyama, 2007; Saad, 2007; Lackenby, 2007. * Baseline virus high IC_{50}, resistant virus IC_{50} 281nM, highly resistant – shift an underestimate. [1] isolates from both seasonal H1N1 and avian H5N1. [2] from avian H5N1 isolates before and after treatment

4.5. Cross Resistance of Mutations Detected by Surveillance

A global Neuraminidase Inhibitor Susceptibility Network (NISN) was established in 1999 to monitor susceptibility of influenza isolates circulating worldwide before the introduction of the neuraminidase inhibitors (1997-1999) and following approval and usage over 3 to 5 years. This network includes key influenza experts from all over the world, many of whom were from the World Health Organization (WHO), Centers for Disease Control (CDC) and Public Health Laboratories. A considerable amount of NA susceptibility monitoring of influenza viruses has also been undertaken by CDC in US, European Surveillance Network for Vigilance against Viral Resistance (VIRGIL), the European Influenza Surveillance Scheme (EISS) and the different World Health Organization (WHO) centers in Australia and Japan. Continued monitoring was considered important to establish whether resistance could become a public health problem, and to determine whether use of neuraminidase inhibitors could lead to changes in HA or NA antigenicity which may compromise vaccine efficacy. In addition, it was considered important for the NISN to establish the best methods to use for monitoring NA susceptibility to ensure development of resistance was monitored correctly. The methods employed include phenotypic susceptibility using NA enzyme assays, followed

by sequencing of the NA gene from assay outliers (outside 95% confidence intervals) [McKimm-Breschkin, 2003; Wetherall, 2003; Zambon, 2001].

To date many thousands of human isolates have been monitored for susceptibility to oseltamivir and zanamivir. In Table 9 below we have included all the zanamivir outliers with shifts in susceptibility above 10, but have not included the oseltamivir outliers unless they showed cross-resistance. None of these isolates were from known NI-treated subjects and included parts of the world where NAIs are not widely used. This suggests that there may be a low level of naturally-occurring resistant variants, the clinical significance of which is not known. The fitness of these isolates has not been studied, and the effect of some mutations on drug-binding is not clear. Only 4 isolates showed dual resistance, and one of these R371K is an active site mutation which may seriously affect fitness. Frequently isolates do not show cross-resistance to both NAIs, which may prove valuable. Clinical cut-offs have not been determined for either zanamivir or oseltamivir and the high local levels of zanamivir may still inhibit some of these isolates.

The work of the NISN is now focusing mainly on monitoring susceptibility of clinical isolates from Japan and other countries where neuraminidase inhibitors are most used.

Table 9 NAI Surveillance Studies - Zanamivir Extreme (>10-fold shift) Outliers in influenza A and B isolates (clinical significance unknown)

Virus Strain	Sequence Changes	Oseltamivir Fold Difference	Zanamivir Fold Difference
A/H1N1/New York/24/2001	G248R I266V	133	68
A/H1N1/Hokkaido/ 15/2002	Y155H + background	123	555
A/H1N1 (2 isolates)	Q136K	0	250
A/H1N1	K120T	0	30
A/H1N1	K143R	10	30
1 B isolate	S250G	0	19
B/HongKong/36 /2005	R371K	248	34
A/H1N1Montana/8/ 2007	D151V/D/	3	123
A/H1N1Argentina/1 35/2005	D151V	1	40
A/H1N1 Canada/270/2007	D151A/D	1	30
A/H1N1Oman/6943/ 2005	D151A	0	22
A/Lyon/765/06	No mutation	0.90	29.98
B/Lyon CHU/8.614/06	D197Y	308.72	14.31

References:- Monto, 2006; Hatakeyama, 2007; Hurt, 2007; Sheu, 2008; Escuret, 2008.

4.6. The Potential for Zanamivir Resistance when used Sub-optimally

Zanamivir inhibits influenza replication and was designed to target the highly conserved active site of the influenza neuraminidase which is essential for release and spread of virus in the respiratory tract. Zanamivir topical application of high drug concentrations produces rapid reductions in virus replication which should limit resistance development. In a study, drug levels in induced sputum were up to 1000 fold greater than the IC_{50} falling to about 50 fold after 24 hours (Table 10) [Cass, 1999; Peng, 2000]. When treated locally with zanamivir, within the first 24-48 hours of infection, virus titers have been shown to reduce rapidly compared to untreated subjects [Barnett, 2000; Boivin, 2000; Puhakka, 2003]. This results in significant rapid reductions in symptoms of influenza with recovery hastened by 1-3 days. The combined activity of zanamivir with local immune responses mean that in immunocompetent subjects, virus replication is rapidly reduced limiting the chance of resistance development. Poor compliance due to irregular use of zanamivir may be less of a problem for resistance due to the high local concentrations achieved after a single inhalation, and the combined efficacy with the local immune responses. Furthermore there is no evidence that resistant viruses are any more virulent than sensitive viruses, and in seasonal influenza they are cleared by immune responses in a similar fashion. With oseltamivir treatment of H5N1 infections there is no clear evidence that development of resistance has contributed to increased deaths. Data from one study suggests that oseltamivir use reduces the mortality rates in seasonal influenza in at risk populations, although there were several limitations in this study [McGeer, 2007]. Therefore if resistant viruses were transmitted to infect high risk individuals then it could be expected that the mortality rate would increase.

Table 10 Zanamivir levels in Sputum following drug administration

Time Post Treatment	Zanamivir Levels in Sputum (ng/ml)	Fold Level above IC_{50}
Immediate	~6,900	> 1,000
6 hours	1,366	> 670
12 hours	304	> 300
24 hours	47	> 50

5. RELENZA MEDKIT DEVELOPMENT PROGRAM

5.1. Program Overview

The Relenza MedKit is being developed as part of a government sponsored program to encourage home stockpiling of anti-viral drugs for use in the event of an announced influenza (flu) pandemic.

The clinical development program for the Relenza MedKit is currently comprised of four (4) robust studies, each designed to answer key questions:

1. Label Comprehension Study
   Can consumers understand the product's use, directions and warnings in the labeling?

2. Human Factors Study
   Can consumers assemble and use the device correctly?

3. Compliance Study
   Can consumers retain the device and not use it during an active flu season (assessed during a 3-month period, during 1 active flu season)?

4. Extended Compliance Study
   Can consumer retain the device and not use it during two flu seasons (assessed during a 15-month period, during 2 active flu seasons)?

These studies are part of a comprehensive program to optimize the product labeling and program plan for the Relenza MedKit. The research has been carefully designed to incorporate the goals and principles that are currently held as best practices for studies supporting a product that will ultimately be used at home by a consumer.

The two protocol approach for the compliance studies was designed to accommodate requests from HHS/CDC to provide data on compliance for more than one flu season. This approach allows data from the 3-month Compliance Study to be included in the sNDA application, while data from the Extended (15-month) Compliance study could be provided as additional supporting data post submission. Instead, FDA have suggested a single protocol approach, in which a study identical in design to the Compliance Study detailed below, but lasting 6 months instead of 3 months, could be conducted instead of two studies. This approach is also acceptable to GSK.

5.2. Label Comprehension Study

Rationale

Label comprehension studies are intended to test the effectiveness of the label. This is a test of the label, not the consumer. Specifically, we will be evaluating the key communication objectives related to the product's intended use, directions for use and warnings. This study is comprised of a one-visit interview related to the product labeling; no drug is dispensed. In this study we will evaluate a general population of normal literacy consumers as well as a general population of low literacy consumers.

Labeling Stimuli

Two (2) labeling stimuli will be tested in this label study:

- The outer Relenza MedKit carton and
- Relenza Quick Guide Patient Brochure.

Study Populations

There are two cohorts planned for this study:

- Normal literacy (NL) General Population, ages 16 and older (n = 175)
- Low literacy (LL) General Population, ages 16 and older (n = 175)

Recruitment

Market research facilities will utilize their site databases for recruitment. Potential participants will be excluded if they have participated in research in the past 12 months, if they work for marketing research or healthcare organizations or have ever been trained as a healthcare professional.

Test Article

- No drug will be utilized in this study. This is a one-visit interview study in which the product labeling will be reviewed and evaluated.

Label Comprehension: Key Methodological Elements

- Broad range of consumers: Because this research is a test of the clarity of the label, we will incorporate a broad range of consumers geographically dispersed throughout the U.S. and in varied socioeconomic categories. Since adolescents become more mobile at the time that they begin to drive and may be in a position to visit their doctor more independently, we have selected ages 16 and above to participate in this study.
- Low Literacy cohort: Literacy will be evaluated for all study participants using the Rapid Estimate of Adult Learning in Medicine (REALM) test or REALM-Teen test. A low literacy cohort has been incorporated into this study so that we can identify any comprehension issues with those consumers of lower literacy (e.g. 7th grade or less).
- Open-ended verbatims with follow-up probes: The most insightful consumer information often comes from open-ended questions in the label comprehension study. This study will have open-ended probes within the questionnaire.
- Non-leading questions: The questions will be designed to be non-leading. That is, the questions will be straightforward and clear without inferences or suggestions.
- Scenario-based: A very effective way of posing label comprehension questions is through third-party scenario questions. This approach is powerful because it requires the consumer to use *judgment* based on the given scenario and the directions/warnings on the label. These types of questions are highly effective in determining if the label is clear.
- Non-biasing approach: The sequencing of questions will be carefully reviewed to avoid response bias in the consumer's responses.
- Detailed Tabulations with Statistical Significance: The data will be tabulated and summarized by correct and incorrect responses for both normal and low literate respondents. Key communications objectives for product use, directions for use and warnings will be coded with net codes for each labeled element. We will be able to evaluate the percentage of correct and incorrect responses for each labeled element. "Acceptable" responses will be evaluated sparingly. This category will be reserved for those responses in which the consumer may not have used the *exact* words on the label, but demonstrated, through answers given during probing, that s/he did, in fact, understand the label directions/warnings.

Primary Objectives

The primary objectives of this study are to evaluate consumer comprehension of the Relenza MedKit package materials for the following communication objectives:

1. To determine if consumers understand the intended product use:
   - Use for pandemic flu
   - Do not use for seasonal flu
2. To determine if consumers understand who should *not* use the MedKit:
   - Children less than 5 years of age for prevention
   - Children less than 7 years of age for treatment
   - Consumers with diagnosed airways disease
   - Consumers who are allergic to any ingredients in Relenza

Secondary Objectives

The secondary objectives of this study are to evaluate consumer comprehension of the MedKit package materials for the following communication objectives:

1. To determine if consumers can make the appropriate decision, based on a scenario, about whether to dose for prevention or treatment:
   - Evaluate for prevention: Adults and children at least 5 years of age who have a household member who has become ill with the flu in the past 2 days
   - Evaluate for treatment: Adults and children at least 7 years of age that have the following symptoms:
     - Fever (100.4^{o} F. and above) within the past 24 hours
     - Cough
2. To determine the correct dose for prevention:
   - For consumers over 5 years of age, inhale 2 times once a day
3. To determine the correct duration of dosing for prevention:
   - 10 days
4. To determine the correct dose for treatment:
   - For consumers over 7 years of age, inhale 2 times in the morning AND 2 times in the evening.
5. To determine the correct duration of dosing for treatment:
   - 5 days
6. To determine if consumers understand when to seek medical attention:
   - Difficulty talking due to breathlessness
   - Medical conditions affecting the immune system, such as:
     - Have had chemotherapy within the last month
   - Continued fever after 48 hours of treatment with non-prescription (OTC) medications.
   - If one has seen a doctor about one of the following conditions in the past one month:
     - Heart disease
   - If the person with flu symptoms does not start to feel better after treatment
   - If the person with flu symptoms has developed heart or lung disease since having the MedKit prescribed.
   - Seizures, confusion or abnormal behavior develops early in the illness
7. Monitoring for flu symptoms:
   - Treat if a fever of at least 100.4^{o} F. and cough develops.
8. Stop Use and Ask a Doctor if:

- Wheezing or shortness of breath develops
- Rash or allergic reaction develops after taking Relenza

9. To determine if consumers know what pandemic flu is

Additional secondary objectives include:

- To conduct a separate analysis of the communication objectives for the Low Literacy and General Population cohort
- To understand the reasons why respondents did not provide the correct answer to questions that addressed the communication objectives.

Inclusion Criteria

Inclusion for this study is determined by cohort.

Cohort 1 – General Population Normal Literacy 16+ (n=175)

To be considered eligible for enrollment in Cohort 1 – General Population Normal Literacy 16+, respondents must:

- Be male or female, of any race
- Be 16 years of age or older
- Individuals 18 + must score 61 or above on the REALM
- Individuals 16-17 must score at or above their grade level on the REALM-Teen

Cohort 2 – General Population Low Literacy 16+ (n=175)

To be considered eligible for enrollment in Cohort 2 - General Population Low Literacy 16+, respondents must:

- Be male or female, of any race
- Be 16 years of age or older
- Individuals 18+ must score 60 or lower on the REALM.
- Individuals 16-17 must score below their grade level on the REALM-Teen

Exclusion Criteria

Respondents in all cohorts will be excluded from the study if:

1) The respondent or anyone in their household is currently employed by any of the following:
   - A marketing or marketing research company
   - An advertising agency or public relations firm
   - A pharmacy or pharmaceutical company
   - A manufacture of medicines
   - A managed care or health insurance company as a healthcare professional
   - A healthcare practice

   2) The respondent has ever been trained or employed as a healthcare professional.
3) They normally wear corrective lenses, contacts or glasses to read and do not have them with them.
4) They have participated in any market research study, product label study or clinical trial in the past twelve (12) months.
5) They cannot read, speak and/or understand English.

Study Design
This will be a multi-site, single visit label, comprehension study conducted at market research sites. Consumers will be recruited from a variety of geographic areas throughout the United States. Each consumer will sign a Confidentiality and Disclosure Agreement (CDA) and then complete the Rapid Estimate of Adult Literacy in Medicine (REALM) or REALM-Teen test to determine literacy. Consumers will then be given an opportunity to read the MedKit materials at their own pace. During this time, the interviewer will step out of the room and allow the consumer to read the materials. Once the consumer indicates that they are finished reading the materials, the interviewer will return and administer the label comprehension interview in a one-on-one interview. The questions will be 3rd party scenario questions that require the consumer to make a judgment about a particular scenario based on the product labeling. After the consumer gives his/her answer, the interviewer will ask a follow-up question ("Why do you say that? or "What led you to that decision?") that will give additional insight into the consumer's reason for their answer. This assures that the consumer is giving the right answer for the right reason. In the event that the consumer's response is incorrect, the follow-up probes will give important insights into the reasons for the incorrect answer.

The data will be collected on questionnaires and tabulated so that the summary results can be analyzed by cohort and by question. Verbatim responses to the follow-up probes will be documented as well.

5.3. Human Factors Study

Rationale
The Human Factors study is intended to test the consumer's ability to correctly manipulate and use the Diskhaler device. In this case, we will be evaluating if the consumer can assemble and use the device correctly, based on the Diskhaler Instruction Sheet. No active drug will be used in this study, but rather the Rotadisks will be filled with air. There are nine (9) specific directions that are outlined in the Instructions. We will be observing consumers, but not directing or influencing them in order to determine if they can correctly follow the nine (9) steps, as directed in the labeling.

Labeling Stimuli
One (1) labeling stimuli will be available to the consumer for this study:
- The Diskhaler Instruction Sheet

Study Populations
- Normal literacy (NL) General Population, ages 16-64 (n = 175)
- Low literacy (LL) General Population, ages 16-64 (n = 175)
- General population of children, ages 5-15, with parent or legal guardian participation/assistance (n=175)

Recruitment
Market research facilities will utilize their site databases for recruitment. Potential participants will be excluded if they have participated in research in the past 12 months, if they work for marketing research or healthcare organizations, have ever been trained as a healthcare professional and if they have previously used this drug. Consumers who

participated in the label comprehension study will not be eligible to participate in the Human Factors Study.

Test Article

- No active drug is utilized in this study. The Diskhaler device and empty (air-filled) Rotadisks will be utilized.

Human Factors: Key Methodological Elements

- Broad range of consumers: Consumers, ages 16+, will be given the opportunity to participate in the study. Since adolescents become more mobile at the time that they begin to drive and may be in a position to visit their doctor more independently, we have selected ages 16+ to participate in this cohort, independently.
- Low Literacy cohort: Literacy will be evaluated for all study participants using the Rapid Estimate of Adult Learning in Medicine (REALM) test or REALM-Teen. A low literacy cohort will be incorporated into this study so that we can identify any comprehension issues with those consumers of lower literacy (e.g. 7th grade or less).
- Children, ages 5 -15: We have included a cohort of children in this study so that we can determine if those children are able to complete step 7 (inhale the medication) correctly. (They will be assisted by a parent/guardian with the other steps).
- Non-intrusive observations: Consumers will be given an opportunity to read and prepare to use the device, as they normally would in real-life. The study coordinator will be recording their actions, but will not be guiding the consumer or answering any questions.
- Follow-up probes: After the human factors assessment is complete, the study coordinator will review the observed actions and ask follow-up questions about any steps that were done incorrectly so that the reasons can be understood.
- Detailed Tabulations with Statistical Significance: The data will be tabulated and summarized by correct and incorrect responses for all cohorts of respondents. Scores for each individual step will be displayed in the data tables. Special attention will be given to steps 5 (puncture the medication blister) and 7 (inhale the medication), which are considered pivotal for correct medication administration. A composite score will also be calculated to assess the overall compliance with all procedural steps. In the event that a consumer was incorrect or incomplete in performing one or more steps, the study coordinator will probe, after the testing is complete, to better understand the reason for the consumer's difficulty with or incorrect performance of any given step.

Primary Objective

1. The primary objective will be to measure subjects' ability to use the Diskhaler correctly based on the Diskhaler Instruction Sheet by performing all 9 steps correctly:

    1. Remove the blue cover
    2. Extend mouthpiece
    3. Remove white tray by pinching raised ridges below dark-brown wheel
    4. Load silver blister disk (found in white canister) into wheel (blister side down) and insert white tray back into Diskhaler body.

5. Lift flap all the way to puncture blister. Medicine is a powder. Keep Diskhaler level for following steps
6. Click flap back in place
7. Breathe out without Diskhaler. Then deeply inhale medicine through mouthpiece
8. Extend white tray. Close tray to rotate to new blister
9. Repeat steps 5 to 8 (you must inhale 2 times [this means using 2 blisters] for 1 full dose).

Secondary Objectives

The secondary objectives will be to:

- To conduct a separate analysis of the primary endpoint for each cohort
- To assess how well participants perform individual steps in order to determine which steps may need to be revised.
- Characterize subpopulations that have difficulty completing all 9 steps correctly.

Inclusion Criteria

Inclusion for this study is determined by cohort.

Cohort 1 – General Population Normal Literacy 16+ (n=175)

To be considered eligible for enrollment in Cohort 1 – General Population Normal Literacy 16+, consumers must:

- Be male or female, of any race
- Be 16 years of age or older
- Be able to read, speak, and understand English
- Individuals 18+ must score 61 or above on the REALM
- Individuals 16-17 must score at or above their grade level on the REALM-Teen

Cohort 2 – General Population Low Literacy 16+ (n=175)

To be considered eligible for enrollment in Cohort 2 - General Population Low Literacy 16+, consumers must:

- Be male or female, of any race
- Be 16 years of age or older
- Be able to read, speak, and understand English
- Individual 18+ must score 60 or lower on the REALM.
- Individual 16-17 must score below their grade level on the REALM-Teen

Cohort 3 – General Population Children age 5-15 (n=175)

To be considered eligible for enrollment in Cohort 3 - General Population Children age 5-15, consumers must:

- Be male or female, of any race
- Be an 18 years of age or older parent or legal guardian of a child age 5 - 15
- Parent or legal guardian must be able to read, speak, and understand English
- Child must be able to hear and understand Parent or Legal Guardian instructions
- REALM test will be conducted (literacy will be recorded)

Exclusion Criteria

Subjects in all cohorts will be excluded from the study if:

1) The subject or anyone in their household is currently employed by any of the following:
   A marketing or marketing research company
   An advertising agency or public relations firm
   A pharmacy or pharmaceutical company
   A manufacture of medicines
   A managed care or health insurance company as a healthcare professional
   A healthcare practice
2) The subject has ever been trained or employed as a healthcare professional.
3) They normally wear corrective lenses, contacts or glasses to read and do not have them with them.
4) They have participated in any market research study, product label study or clinical trial in the past 12 months.
5) They have underlying airways disease such as chronic obstructive pulmonary disease (COPD), chronic bronchitis, asthma or emphysema.
6) They have previous experience using the Relenza Diskhaler®.

Study Design

This will be a multi-site, single visit, human factors study. Study subjects will be recruited from a variety of geographic areas throughout the United States. Each subject will sign a Confidentiality and Disclosure Agreement (CDA) and then complete the Rapid Estimate of Adult Literacy in Medicine (REALM) or REALM-Teen test to determine literacy. After the REALM or REALM-Teen test and prior to performing the use steps, each subject will have access to the approved Relenza Diskhaler Instruction Sheet to read at their own pace; they will be permitted to refer back to the materials as often as desired during the test. Subjects will be given the opportunity to read the Relenza Diskhaler Instructions Sheet and to practice with the Diskhaler prior to actually using the device, as is recommended in the product labeling. When the subject indicates s/he is ready, the Interviewer will re-enter the room and begin the inerview. Subjects will be asked to demonstrate the use of the device as if they were preparing to use it. The subject will be notified that, for the purposes of this study, the device contains only air-filled blisters, not the actual Relenza medicine. The coordinator will record the subject's performance during the device use. At the end of the observation period, any incorrect actions will be reviewed with the consumer to better understand the reason for any incorrect or incomplete actions related to the Instructions for using the device.

5.4. Compliance Study

If the single compliance study approach suggested by FDA can be utilized, this study will be extended from 3 months to 6 months, and the Extended Compliance study will not be required.

Rationale

This is a targeted compliance study. The study will be conducted in two parts: (1) 12-week, at-home product retention evaluation and (2) pandemic scenario evaluation. This

study is intended to incorporate aspects of the pandemic flu stockpiling effort being created by HHS, CDC and FDA. The following anticipated program elements have been designed into this study:

- Awareness: Expose consumers to the concept of home stockpiling of drug, in the form of the Relenza MedKit, for prevention and treatment of pandemic flu.
- Evaluation: Consult a healthcare provider to learn more, be evaluated for appropriateness for use of the drug, and obtain the Relenza MedKit.
- Product Retention at Home: Be in a state of readiness for a flu pandemic by storing the product at home with all enclosed instructions, practice materials and brochures.
- Decision-Making: Make the decision about when/if to use the Relenza Medkit.

The subject will be given an opportunity to become aware of the MedKit concept and to be evaluated by a healthcare professional (HCP), such as a physician or nurse practitioner (NP), in order to determine if s/he is an appropriate candidate for the MedKit. If appropriate, the subject will be given the opportunity to take the product home to stockpile in the event of a local flu pandemic. To further assess the clarity of the labeling and to better understand consumer behavior, the MedKit will be in the subject's home during one active flu season, a 12-week product retention period. During this time, the subject will not be contacted by study staff, except to schedule Visit 2. After the 12-week, in-home, product retention period, consumers will return to the research site. At this time, the subject's intended response to a pandemic will be evaluated based on a pandemic scenario.

At Visit 2, subjects will be assigned to one of two pandemic scenarios. They will be asked to imagine that one of these scenarios has just occurred and to describe the actions that they would take in that particular scenario. These scenarios are as follows:

1. Pandemic flu in the U.S. (do not use the MedKit)
2. Pandemic flu confirmed/communicated in their local area (use the MedKit)

Subjects will verbalize their intended actions based on their judgment and the product labeling. After verbalizing their intended course of action, the study staff will conduct follow-up probes to further understand the reason behind any incorrect or incomplete responses.

Labeling Stimuli

Labeling that is anticipated at the time of commercialization, will be available to the consumer. At a minimum, this will consist of the following:

- Exterior package labeling
- Quick Guide Consumer Brochure
- Diskhaler and Rotadisks
- Diskhaler Instruction Sheet

Study Populations

- Adult population, ages 16+ (n=150)
- Pediatric population, ages 5-15, assisted by parents or guardians, (n=150)

Recruitment

- Subjects will be recruited via calls to site databases and through community outreach (flyers/concept boards).
- Consumers who are interested in learning more about a healthcare product that may help them prevent or treat flu, will be screened and if the screening criteria are met, the consumer will be invited to a local research center.
- Since a healthcare provider must evaluate if the consumer is appropriate for the use of this drug, the sites will be clinical research facilities.

Test Article

Relenza MedKit (containing components listed under 'labeling stimuli')

Compliance Study: Key Methodological Elements

- Unsupervised home use: The consumer will be sent home with the MedKit, as they would do if the MedKit were to become available. In this study, we are evaluating if the consumer chooses not to use the product for seasonal flu.
- Reasons for non-compliance: Data related to non-compliant behaviors will be cross-tabulated for "Reasons" so that trends and patterns can be identified.
- Evaluation of safety outcomes: Safety will be evaluated by assessing and following up on adverse and serious adverse events.

Primary Objective

- Demonstrate the subject's ability to make the appropriate decision about when to use the Relenza MedKit (only for the purpose of preventing or treating pandemic influenza).

Co-Primary Objectives

- Demonstrate the subject's ability to appropriately retain/locate the Relenza MedKit containing all 5 unused Rotadisks.
- Evaluate the subject's intended actions based verbal responses to a pandemic scenario.

Secondary objectives:

- To conduct a separate analysis of the primary and co-primary endpoints for each cohort
- To understand the reasons:
  - why participants did not make the appropriate decision when to use the Relenza MedKit
  - why participants were unable to retain and locate the Relenza MedKit containing all 5 unused Relenza Rotadisks
  - why participants had intended actions based on verbal responses to a pandemic that were incorrect
- To assess if members of the household who should not have taken Relenza took Relenza and to find out the reasons why.

Inclusion Criteria

To be considered eligible for the study, subjects must meet the following inclusion criteria:

1. Adults and adolescents (ages 16+) who state an interest in stockpiling the Relenza MedKit in the event of pandemic flu;
2. Parents of children (ages 5-15) who state an interest in stockpiling the Relenza MedKit for their child/children in the event of pandemic flu;
3. Are able to read and understand English; and
4. Are willing to participate in all study procedures and voluntarily sign an Informed Consent/Assent document.

Exclusion Criteria

Subjects meeting the following criteria will be excluded from the study:

1. The subject or anyone in their household is currently employed by any of the following:
    - A marketing or marketing research company, advertising agency or public relations firm
    - A pharmacy, pharmaceutical company, manufacturer of medicines
    - A managed care or health insurance company as a healthcare professional
    - A healthcare practice
2. The subject has ever been trained or employed as a healthcare professional.
3. The subject normally wears corrective lenses, contacts or glasses to read and does not have them with them.
4. The subject has participated in any research study in the past 6 months.
5. The subject has previous experience using the Relenza Diskhaler.
6. The subject has underlying airways disease such as chronic obstructive pulmonary disease (COPD), chronic bronchitis, asthma or emphysema.
7. The subject is pregnant or breastfeeding.

Study Design and Methodology

This is a multi-center, open-label compliance study that will evaluate a consumer's ability to retain the MedKit at home and avoid use during an active flu season. In addition, the subject's ability to make the appropriate decisions in a pandemic will be evaluated through a pandemic scenario given at Visit 2. At this time, the subject will be asked to verbalize the actions that they would take in the given scenario based on their judgment and the product labeling. The product and labeling will remain available to the subject during the scenario phase of the study. This study will be conducted in approximately 10-20 clinical research sites within the United States.

At Visit 1, subjects will read and sign a Confidentiality Agreement and review a product concept based on a poster or flyer resembling what may be used in physician's offices and retail clinics when the MedKit is available. Subjects who are 16 years of age and older will read and sign an IRB-approved Informed Consent Form (ICF). Subjects will be given ample opportunity to read the consent form and have all questions regarding study conduct answered prior to signing the consent form. If the subject is 16-17 years of

age, a parent or legal guardian will have to sign the ICF. If the subject is 8-15 years of age, s/he must provide written assent. Children 7 years of age or less must provide verbal assent, if able, or will be covered by the parent/legal guardian's signature on the child's assent. Each subject will be provided with a copy of the ICF and/or assent to retain for his/her records. Signatures on the ICF and assent will be witnessed.

Site Staff will administer the Rapid Estimate of Adult Literacy in Medicine (REALM) Test to adults and the Rapid Estimate of Adult Literacy in Medicine (REALM-TEEN) Test to adolescents. Site Staff will confirm the inclusion/exclusion criteria and collect a brief medical history, medication history and demographics. A pregnancy test will be performed for women of child-bearing potential. Site staff will provide product information/education to the subject, similar to what will be available to HCPs when the MedKit is available.

The subjects will take the product home for a 12-week in-home product retention period (Days 1-84), that will take place during an active flu season. The only contact that the study staff will have with the subject during this time will be to schedule Visit 2. At Visit 2, (Day 85 +/- 3 days), the subject will be given one of two pandemic scenarios and asked to verbalize their intended response to study staff. The product and product labeling will remain in full view of the subject so that they can refer to any materials, as they would in real-life, as they determine and describe their intended course of action. Study staff will record subject responses. Any incorrect or incomplete actions will be further probed at the completion of the scenario exercise, so that the reasons for the incorrect responses can be further understood. The subject will undergo a post-treatment medical history and medication history to determine if any medications or medical conditions changed during the product retention period. Subjects will be queried about any changes in health or potential adverse events that may have occurred during the product retention phase of the study. Subjects may complete a post-study questionnaire. Finally, site staff will collect the remaining product. In the event that there are any adverse events, an optional, Visit 3, can be scheduled. Adverse events will be followed to resolution.

5.5. Extended Compliance Study

Rationale

This study will not be conducted if the single compliance study approach suggested by FDA can be utilized. This is a targeted, extended compliance study designed to determine if consumers can retain the Relenza MedKit in their homes for an extended (approximately 15 month) period, and make the appropriate decisions about whether or not to use the Relenza MedKit. This study is similar to the Compliance Study discussed above with two (2) exceptions:

- The in-home retention period will be 15 months for this study vs. 3 months for the compliance study. This extended period of time allows for the evaluation of consumer behavior related to product retention or use during at least two flu seasons.
- The pandemic scenarios will not be administered in this study. This is a secondary objective of the Compliance study discussed above.

6. SUMMARY OF POTENTIAL RISKS AND BENEFITS OF A RELENZA MEDKIT

Understanding that there are potential risks and benefits of a Relenza MedKit for home stockpiling use, we highlight some of the key issues below.

Potential Risks

- Safety: known adverse events as described in the label, including bronchospasm.
- Use in patient populations other than those recommended in the label
- Change in medical conditions over time, with no reassessment of risk/benefit
- Inappropriate use for non-pandemic influenza situations
- Unknown medical benefit of zanamivir against pandemic strains of influenza
- Increased potential for generation of viral resistance to zanamivir, secondary to sub-optimal use.
- Inappropriate storage of MedKit resulting in decreased potency.
- Potential for unsafe storage of the MedKit leading to access by unintended users, such as children.

Potential Benefits

- Greater access to antiviral medications for a larger proportion of the general public.
- More immediate access to antiviral medications for a larger proportion of the general public.
- Access to potentially life-saving medication in situations where ready access to healthcare services may be severely limited.
- Access to MedKits in the event of central distribution failure of government stockpiles
- Maintains social distancing, while allowing access to antiviral medication.
- A potential medical benefit of zanamivir against pandemic strains of influenza, including survival
- Augments the capacity of antivirals to contribute to the containment of pandemic spread
- Provides a bridge to vaccination during lag time prior to vaccine availability and onset of vaccine efficacy.

7. CONCLUSION

GSK is responsive to the public health community's call for new and creative approaches to assuring ready access by appropriate lay individuals in the US to antiviral drugs for prevention or treatment of influenza. A Relenza MedKit for home stockpiling for pandemic influenza may be a useful addition to pandemic preparedness plans, pending successful design and evaluation of the MedKit. Proper use instructions, both for the device and for the appropriate situations for use, are critical to ensure the safety of the patient and the minimization of inappropriate use that might lead to the generation of antiviral resistance and other adverse consequences.

8. REFERENCES

American College of Physicians (ACP). The Health Care Response to Pandemic Influenza. Philadelphia: American College of Physicians; 2006: Position Paper. (Available from American College of Physicians, 190 N. Independence Mall West, Philadelphia, PA 19106.)

Barnett J M, Cadman A, Burrell F M, Madar S H, Lewis A P, Tisdale M, and Bethell R. 1999. *In Vitro* Selection and Characterisation of Influenza B/Beijing/1/87 Isolates with Altered Susceptibility to Zanamivir. Virology 265, 286-295

Barnett JM, Cadman A, Gor D, Dempsey D, Walters M, Candlin A, Tisdale M, Morley PJ, Owens IJ, Fenton RJ, Lewis AP, Claas ECJ, Rimmelzwaan GF, De Groot R, Osterhaus ADME. 2000. Zanamivir Susceptibility Monitoring and Characterization of Influenza Virus Clinical Isolates Obtained during Phase II Clinical Efficacy Studies. Antimicrobial Agents And Chemotherapy, 44 (1): 78–87.

Baz M, Abed Y, Boivin G. Characterization of drug-resistant recombinant influenza A/H1N1 viruses selected in vitro with peramivir and zanamivir. Antiviral Research 2007; 74: 159-162.

Beigel JH, Farrar J, Han AM, Hayden FG, Hyer R, de Jong MD, Lochindarat S, Nguyen TK, Nguyen TH, Tran TH, Nicoll A, Touch S, Yuen KY; Writing Committee of the World Health Organization (WHO) Consultation on Human Influenza A/H5. N Engl J Med. 2005 Sep 29;353(13):1374-85

Blick T J, Tiong T, Sahasrabudhe A, Varghese J N, Colman P M, Hart G J, Bethell R C, And Mckimm-Breschkin J L. 1995. Generation and Characterization of an Influenza Virus Neuraminidase Variant with Decreased Sensitivity to the Neuraminidase-Specific Inhibitor 4-Guanidino-Neu5Ac2en. Virology 214, 475–484.

Blick T J, Sahasrabudhe A, McDonald M, Owens I J, Morley P J, Fenton R J, and McKimm-Breschkin J L. 1998. The Interaction of Neuraminidase and Hemagglutinin Mutations in Influenza Virus in Resistance to 4-Guanidino-Neu5Ac2en. Virology 246, 95–103.

Boivin G, Goyette N, Hardy I, Aoki F, Wagner A, and Trottier S. 2000. Rapid Antiviral Effect of Inhaled Zanamivir in the Treatment of Naturally Occurring Influenza in Otherwise Healthy Adults The Journal of Infectious Diseases;181:1471–4.

Cass L M R, Brown J, Pickford M, Fayinka S, Newman S P, Johansson C J and A Bye. 1999. Pharmacoscintigraphic Evaluation of Lung Deposition of Inhaled Zanamivir in Healthy Volunteers. Clin Pharmacokinet; 36 Suppl. 1: 21-31

CDC's Division of Strategic National Stockpile Emergency MedKit Evaluation Study Summary – Background, Key Results, and Next Steps, November 2007. Available at

http://www.bt.cdc.gov/agent/anthrax/prep/pdf/medkit-evaluation-summary-2007.pdf. Accessed September 8, 2008.

Collins P J, Haire L F, LinY P, Liu J, Russell R J, Walker P A, Skehel J J, Martin S R, Hay A J and Gamblin S J (2008). The mechanism of H5N1 Influenza resistance to Tamiflu and implications for drug stockpiles. Nature 453(7199): 1258-1261.

Escuret V, Frobert E, Bouscambert-Duchamp M, Sabatier M, Grog I, Valette M, Lina B, Morfin F, Ferraris O. (2008). Detection of human influenza A (H1N1) and B strains with reduced sensitivity to neuraminidase inhibitors. J Clin Virol, **41:** 25-28.

Gubareva L V, Bethell R, Hart G J, Murti K G, Penn C R, And Webster R G. 1996a. Characterization of Mutants of Influenza A Virus Selected with the Neuraminidase Inhibitor 4-Guanidino-Neu5Ac2en. Journal Of Virology, 70: 1818–1827.

Gubareva LV, Bethell RC, Penn CR, Webster RG. In vitro characterization of 4-guanidinoNeu5Ac2en-resistant mutants of influenza A virus. 1996b. In: Brown LE, Hampson AW, Webster RG, Eds. Option for the control of influenza III, Amsterdam: Elsevier, :753-760

Gubareva L V, Robinson M J, Bethell R C, And Webster R G. 1997. Catalytic and Framework Mutations in the Neuraminidase Active Site of Influenza Viruses That Are Resistant to 4-Guanidino-Neu5Ac2en. Journal Of Virology, 71: (5) 3385–3390.

Gubareva LV, McCullers JA, Bethell R, Webster RG. Characterization of human influenza A/Hong Hong/156/97 (H5N1) virus in a mouse model and protective effect of zanamivir on H5N1 infection in mice. J Infect Dis. 1998a;178:1592-6.

Gubareva L V, Matrosovich M N, Brenner M K, Bethell R C, and Webster R G. 1998b. Evidence for Zanamivir Resistance in an Immunocompromised Child Infected with Influenza B Virus. Journal of Infectious Diseases 178:1257–62

Hatakeyama S, Sugaya N, Ito M, Yamazaki M, Ichikawa M, Kimura K, Kiso M, Shimizu H, Kawakami C, Koike K, Mitamura K, Kawaoka Y. 2007. Emergence of Influenza B Viruses With Reduced Sensitivity to Neuraminidase Inhibitors JAMA,297: 1435-1442.

Herlocher ML, Carr J, Ives J, Elias S, Truscon R, Roberts N, Monto AS. Influenza virus carrying an R292K mutation in the neuraminidase gene is not transmitted in ferrets. Antiviral Res 2002; 54: 99-111.

Hurt A and Barr IG 2007 Novel Mutations in the '150-cavity'of N1 neuraminidase Confer Reduced Sensitivity to the Neuraminidase Inhibitors Abstract 067 and Oral Presentation at Options for the Control of Influenza VI Toronto 2007.

Koopmans M, Wilbrink B, Conyn M, Natrop G, van der Nat H, Vennema H, Meijer A, van Steenbergen J, Fouchier R, Osterhaus A, Bosman A. Transmission of H7N7 avian influenza A virus to human beings during a large outbreak in commercial poultry farms in the Netherlands. Lancet. 2004 Feb 21;363(9409):587-93.

Lackenby A, Siqueira M, Elliot A, Alvarez A, Baldevarona J, Bremner J, Ellis JS and Zambon M, Persistent Influenza Infection and Antiviral Drug Resistance in Immunocompromised Patients. Abstract and Poster P931 at Options for the Control of Influenza VI Toronto 2007.

Lackenby A, O Hungnes, S G Dudman, A Meijer, W J Paget, A J Hay, M C Zambon 2008. Emergence of resistance to oseltamivir among influenza A(H1N1) viruses in Europe. Eurosurveillance, Volume 13, Issue 5, 31 January 2008 Rapid communications

Le QM, Kiso M, Someya K, Sakai YT, Nguyen H, Nguyen KHL, Pham D, Ngyen HN, Yamada S, Muramoto Y, Horimoto T, Takada A, Goto H, Suzuk T, Suzuki Y, Kawaoka Y. Isolataion of drug-resistant H5N1 virus. Nature 2005; 437: 1108.

Leneva IA, Goloubeva O, Fenton RJ, Tisdale M, Webster RG. Efficacy of zanamivir against avian influenza A viruses that possess genes encoding H5N1 internal are pathogenic in mammals. *Antimicrob Agents Chemother.* 2001;45:1216-24.

McGeer A, Green K A, Plevneshi A, Shigayeva A, Siddiqi N, Raboud J, and Low D E. 2007. Antiviral Therapy and Outcomes of Influenza Requiring Hospitalization in Ontario, Canada. Clinical Infectious Diseases; 45:1568–75.

Mckimm-Breschkin J L, Blick T J, Sahasrabudhe A, Tiong T, Marshall D, Hart G J, Bethell R C, And Penn C R. 1996. Generation and Characterization of Variants of NWS/G70C Influenza Virus after *In Vitro* Passage in 4-Amino-Neu5Ac2en and 4-Guanidino-Neu5Ac2en. Antimicrobial Agents And Chemotherapy, 40 (1): 40–46.

Mckimm-Breschkin J L, Sahasrabudhe A, Blick T J, Mcdonald M, Colman P M, Hart G J, Bethell R C, And Varghese J N. 1998. Mutations in a Conserved Residue in the Influenza Virus Neuraminidase Active Site Decreases Sensitivity to Neu5Ac2en-Derived Inhibitors. Journal Of Virology, 72 (3): 2456–2462.

McKimm-Breschkin J T Trivedi, A Hampson, A Hay, A Klimov, M Tashiro, F Hayden, and M Zambon 2003. Neuraminidase Sequence Analysis and Susceptibilities of Influenza Virus Clinical Isolates to Zanamivir and Oseltamivir. Antimicrobial Agents And Chemotherapy Vol. 47, No. 7 p. 2264–2272

Mishin VP, Hayden FG, Gubareva L, 2005. Susceptibilities of Antiviral –Resistant Influenza Viruses to Novel Neuraminidase Inhibitors AAC: 49: 4515-4520.

Monto AS, Macken C, McKimm-Breschkin JL, Hampson AW, Hay A, Klimov A, Tashiro M, Webster RG, Aymard M, Hayden F, Zambon M. 2006. Influenza viruses resistant to the neuraminidase inhibitors detected during the first three years of their use. AAC; 50: 2395-2402.

Oner AF, Bay A, Arslan S, Akdeniz H, Sahin HA, Cesur Y, Epcacan S, Yilmaz N, Deger I, Kizilyildiz B, Karsen H, Ceyhan M. Avian influenza A (H5N1) infection in eastern Turkey in 2006. N Engl J Med. 2006 Nov 23;355(21):2179-85.

Peng A W, Milleri S, And Stein D S. 2000. Direct Measurement of the Anti-Influenza Agent Zanamivir in the Respiratory Tract following Inhalation. Antimicrobial Agents And Chemotherapy, 44 (7): 1974–1976.

Puhakka U, Lehti H, Vainionpää R, Jormanainen V, Pulkkinen M, Sharp S, Kerr C, Dempsey M, Ring CJA, Ward C, and Tisdale M. (2003) Zanamivir: A significant reduction in viral load during treatment in military personnel with influenza. Scand J Infect Dis **35**: 52-58.

Saad MD, Boynton BR, Earhart KC, Mansour MM, Niman HL, Elsayed NM, Nayel AI, AbdelghaniAS, Essmat HM, Labib EM, Ayoub EA, Monteville MR. Detection of Oseltamivir Resistance Mutation N294S in Humans With Influenza A H5N1. Abstract P909. Options for Control of Influenza meeting, Toronto 2007.

Sheu T G, Deyde V M, Okomo-Adhiambo M, Garten R J, Xu X, Bright R A, Butler E N, Wallis T R, Klimov A I, and Gubareva L V. 2008. Surveillance for Neuraminidase Inhibitor Resistance among Human Influenza A and B Viruses Circulating Worldwide from 2004 to 2008. Antimicrobial Agents And Chemotherapy, 52: 3284–3292.

Smith BJ, McKimm-Breshkin J L, McDonald M, Fernley R T, Varghese J N, and Colman P M. 2002. Structural Studies of the Resistance of Influenza Virus Neuramindase to Inhibitors. *J. Med. Chem.*, *45,* 2207-2212.

Staschke KA, Colacino JM, Baxter AJ, Air GM, Bansal A, Hornback WJ, Munroe JE, Laver WG. 1995. Molecular basis for the resistance of influenza viruses to 4-guanidino-Neu5Ac2en. Virology; 214: 642-646

Tran TH, Nguyen TL, Nguyen TD, Luong TS, Pham PM, Nguyen VC, Pham TS, Vo CD, Le TQ, Ngo TT, Dao BK, Le PP, Nguyen TT, Hoang TL, Cao VT, Le TG, Nguyen DT, Le HN, Nguyen KT, Le HS, Le VT, Christiane D, Tran TT, Menno de J, Schultsz C, Cheng P, Lim W, Horby P, Farrar J; World Health Organization International Avian Influenza Investigative Team. Avian influenza A (H5N1) in 10 patients in Vietnam. N Engl J Med. 2004 Mar 18;350(12):1179-88.

US Department of Health and Human Services (US HHS) Pandemic Influenza Plan November 2005. http://www.hhs.gov/pandemicflu/plan/pdf/HHSPandemicInfluenzaPlan.pdf. Accessed September 8, 2008.

US Department of Health and Human Services (US HHS). Antivirals – State Allocations. 6-27-2008. http://www.pandemicflu.gov/plan/states/antivirals.html. Accessed September 19, 2008.

Varghese J N, Smith P W, Sollis S L, Blick T J, Sahasrabudhe A, McKimm-Breschkin J L and Colman P M. 1998. Drug design against a shifting target: a structural basis for resistance to inhibitors in a variant of influenza virus neuraminidase. Structure, 6(6): 735–746.

Wetherall NT, Trivedi T, Zeller J et al. Evaluation of neuraminidase enzyme assays using different substrates to measure susceptibility of influenza virus clinical isolates to neuraminidase inhibitors: report of the neuraminidase inhibitor susceptibility network. J Clin Microbiol 2003.

WHO 2008 Influenza A(H1N1) virus resistance to oseltamivir - 2008 influenza season, Southern Hemisphere, 18 July 2008. Available at: http://www.who.int/csr/disease/influenza/H1N1webupdate18072008.pdf. Accessed September 8, 2008.

Zambon, M., and F. G. Hayden. 2001. Position statement; global neuraminidase inhibitor susceptibility network (NISN). Antivir. Res. **49:**147–156.

Zürcher T, Yates P J, Daly J, Sahasrabudhe A, Walters M, Dash L, Tisdale M and McKimm-Breschkin J L. 2006. Mutations conferring zanamivir resistance in human influenza virus N2 neuraminidases compromise virus fitness and are not stably maintained *in vitro*. Journal of Antimicrobial Chemotherapy 58, 7

APPENDIX 1: RELENZA MEDKIT – COMPONENTS OF LABELING

Outer Carton (Exterior Package Labeling)

PRINT SIDE

LINE INDICATES COATING

Use RELENZA ONLY if pandemic flu is in your area and you have symptoms or have been exposed to someone ill with the flu within the last 2 days. Do NOT use for seasonal flu.

PANDEMIC FLU READINESS KIT

RELENZA® (ZANAMIVIR) INHALATION POWDER MEDKIT™

Your Name _____

TREATMENT									
Day 1		Day 2		Day 3		Day 4		Day 5	
AM	PM	AM	PM	AM	PM	AM	PM	AM	PM

PREVENTION				
Day 1 AM	Day 2 AM	Day 3 AM	Day 4 AM	Day 5 AM
Day 6 AM	Day 7 AM	Day 8 AM	Day 9 AM	Day 10 AM

Mark each family member's RELENZA® MedKit box with his/her name.

019297

Use RELENZA ONLY if pandemic flu is in your area and you have symptoms or have been exposed to someone ill with the flu within the last 2 days. Do NOT use for seasonal flu.

RELENZA® Dose Tracker

It's very important that you keep track of which family member gets prevention or treatment, or does not use RELENZA.

Your Name _____

Prevention ☐ Treatment ☐ Do Not Use ☐

PANDEMIC FLU READINESS KIT

RELENZA® (ZANAMIVIR) INHALATION POWDER MEDKIT™

Use RELENZA ONLY if pandemic flu is in your area and you have symptoms or have been exposed to someone ill with the flu within the last 2 days. Do NOT use for seasonal flu.

This RELENZA MedKit was prescribed just for:

Your Name Here:

Do NOT share the contents of this RELENZA MedKit with others.

PANDEMIC FLU READINESS KIT

RELENZA® (ZANAMIVIR) INHALATION POWDER MEDKIT™

Contains 5 RELENZA ROTADISKS® each containing four 2-mg blisters and one DISKHALER inhalation device.

Do NOT Swallow Powder. Powder is Inhaled Through Mouth.

Use RELENZA ROTADISKS with the DISKHALER inhalation device only.

See enclosed Patient Information and Patient Instruction for Use.

Store at 20-25°C (Excursions permitted to 15°C-30°C) [See USP Controlled Room Temperature].

Keep out of the reach of children.

10 Doses (20 Inhalations)

Expires December XX, XXXX

Lot Number XXX-XXX

Manufactured for: GlaxoSmithKline Group of Companies. All rights reserved. Printed in USA. IL-XX-XXX

August 2006

Kwik

PANDEMIC FLU READINESS KIT

RELENZA® (ZANAMIVIR) INHALATION POWDER MEDKIT™

Use RELENZA ONLY if pandemic flu is in your area and you have symptoms or have been exposed to someone ill with the flu within the last 2 days. Do NOT use for seasonal flu.

GlaxoSmithKline

Use RELENZA ONLY if pandemic flu is in your area and you have symptoms or have been exposed to someone ill with the flu within the last 2 days. Do NOT use for seasonal flu.

PANDEMIC FLU READINESS KIT

RELENZA® (ZANAMIVIR) INHALATION POWDER MEDKIT™

To Treat and/or Prevent Flu Only

Open Right Away—To Help You Prepare

- Read RELENZA MedKit Quick Guide
- Try Practice-DISKHALER® and Practice-ROTADISKS®
- Carry Reminder Card in your wallet for tips in the event of pandemic flu

For the latest pandemic flu information, visit www.pandemicflu.gov or call 1-800-CDC-INFO.

You are encouraged to report negative side effects of prescription drugs to the FDA.

Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

GlaxoSmithKline

HOWELL PACKAGING Division of F.M. HOWELL & COMPANY BOX 286, ELMIRA, NY 14902 (607)734-6291

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Quick Guide Patient Brochure

PANDEMIC FLU READINESS KIT

RELENZA® (ZANAMIVIR) INHALATION POWDER MEDKIT™

How to Use Your RELENZA MedKit for Pandemic Flu

Quick Guide

STOP! Before you use the RELENZA in this MedKit:
WAIT until your local or state health department says that pandemic flu is in your area.
READ this Quick Guide to learn how to recognize pandemic flu symptoms.

For the latest pandemic flu information, visit **www.pandemicflu.gov**, or call **1-800-CDC-INFO**.

See Important Safety Information inside.

The **GREEN** pages have **YES** or **NO** questions that will help you identify pandemic flu and help you decide what type of medical care is needed.

IMPORTANT WARNING!

This MedKit ***IS*** intended for:

- Use in the event of an announced flu pandemic *(announced by state or local health department officials)*

This MedKit is ***NOT*** intended for:

- Treatment or prevention of seasonal flu
- Anyone who has airway diseases such as asthma or emphysema
- Anyone who has an allergy to lactose (RELENZA contains lactose)
- Children under 7 years of age (for treatment dosing)
- Children under 5 years of age (for prevention dosing)

What's Inside This Quick Guide?

What Is Pandemic Flu? 4

What Is the RELENZA MedKit? 5

Identifying People at Risk for Pandemic Flu 6

Recognizing a Medical Emergency 7

Knowing if People With Health Concerns Need Medical Care 8

Identifying Pandemic Flu 10

Taking Steps to Feel Better 11

Dosing Information 12

When to Contact Your Doctor and/or Stop Taking RELENZA 14

How Do I Use My RELENZA DISKHALER? 16

Important Safety Information About RELENZA 18

FAQs 19

Upon opening, if you are missing any component of this kit, please call GlaxoSmithKline at 1-800-[to come].

RELENZA®
(ZANAMIVIR) INHALATION POWDER

What Is Pandemic Flu?

Pandemic flu is different from seasonal flu.

Seasonal flu is a common viral illness of the upper respiratory tract with symptoms that include fever, cough, and extreme tiredness. Each year, people catch it and spread it to others, so it's smart to get a flu shot every year.

Pandemic flu is a brand-new type of flu that can be deadly.

Because it's new, our bodies have little or no defense against it. It can cause serious illness and easily spread from person to person. It can even spread around the world. Like seasonal flu, pandemic flu spreads when a person with the flu coughs or sneezes, and tiny droplets land on the mouth or nose of others. Or if people touch these droplets on an object and then touch their mouth, they can get the flu. That's why it's important to wash your hands often.

People with pandemic flu can spread it for several days (possibly up to a week or longer) after they get sick, even when taking medicine. During this time, help prevent the spread of flu in your family by making a "sick room" at home and having one family member care for the sick person. To limit the spread of flu in the community, the sick person should stay home. If the person has to go out, he or she should wear a hospital mask. Other family members should also stay home because they may have the flu, even if they don't feel sick.

Visit **www.pandemicflu.gov** to learn more about pandemic flu.

What Is the RELENZA MedKit?

The RELENZA MedKit is designed to be kept at home for use in the event of an announced flu pandemic. Inside are the tools and information you'll need in the event of pandemic flu. It is for emergency use only. If you have flu symptoms but there is no pandemic, see your doctor for treatment.

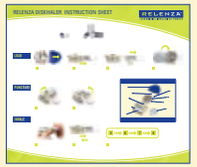
You'll also find the medicine RELENZA inside. RELENZA belongs to a group of drugs called antivirals. These drugs target the flu virus and help keep it from spreading inside your body. RELENZA can be used for prevention and/or treatment of flu.

- Treatment: If taken within the first 2 days of feeling ill, RELENZA can cut down the time you'll suffer from symptoms
- Prevention: If taken within 2 days of contact with someone ill with the flu, RELENZA can help prevent you from getting sick

What's Inside Your RELENZA MedKit?

Practice-DISKHALER® & ROTADISK®s
Start practicing today. Get used to using your DISKHALER. The Practice-DISKHALER does not have any drug inside—it's for practice only.

Instruction Sheet—Follow these step-by-step instructions on how to use your DISKHALER and ROTADISKs.



Reminder Card—Quick tips in the event of pandemic flu.

RELENZA DISKHALER & ROTADISKs—Found in the small box labeled RELENZA. Includes real medicine; use only during a pandemic.

RELENZA®
(ZANAMIVIR) INHALATION POWDER

Identifying People at Risk for Pandemic Flu

The following pages are for helping you determine if you have been exposed to pandemic flu and what measures to take.

Has the local or state health department said that pandemic flu has been detected in your area?

☐ YES ☐ NO

Have you or any member of your household very recently developed one or more of these symptoms?

☐ Fever	☐ Runny nose	☐ Muscle aches
☐ Chills	☐ Sore throat	☐ Extreme tiredness
☐ Cough	☐ Shortness of breath	☐ Headache

☐ YES ☐ NO

If you have checked ANY of the NO boxes, you don't need the MedKit now. Stay alert for pandemic flu announcements and flu symptoms.

If you have checked BOTH of the YES boxes above, **go to page 7.**

Recognizing a Medical Emergency

Does the person with symptoms show ANY of these signs?

- ☐ Difficulty talking, due to breathlessness
- ☐ For babies, not eating or drinking due to breathlessness
- ☐ Blue or gray skin color around the mouth
- ☐ Chest pain
- ☐ Being less awake or responsive than you expected
- ☐ Appears confused or disoriented

☐ YES ☐ NO

If you checked the YES box, call 911 or take the person to the nearest Emergency Room.

If you checked the NO box, **go to page 8.**

RELENZA®
(ZANAMIVIR) INHALATION POWDER

Knowing if People With Health Concerns Need Medical Care

Does the person with symptoms have ANY of the following?

- ☐ Shortness of breath (fast or difficult breathing)
- ☐ Severe vomiting
- ☐ Medical condition affecting the immune system, such as:
  - —Recent bone marrow transplant
  - —Leukemia or lymphoma
  - —HIV infection or AIDS
  - —Chemotherapy within the last month
  - —Taking oral steroids for more than 1 week
- ☐ Aged less than 2 years or 70 years and older

☐ **YES** ☐ **NO**

Has the person with symptoms had to see a doctor

1) In the last month for any ONE of these health conditions?

OR

2) Within the last 6 months for any TWO of these health conditions?

- ☐ Heart disease
- ☐ Kidney disease
- ☐ Lung disease (such as asthma or emphysema)
- ☐ Liver disease
- ☐ Diabetes

☐ **YES** ☐ **NO**

If you checked ANY of the YES boxes, or if you think that medical care is needed, contact a doctor or go to an Emergency Room.

If you checked BOTH the NO boxes, **go to page 10.**

RELENZA®
(ZANAMIVIR) INHALATION POWDER

Identifying Pandemic Flu

Does the person have BOTH of these symptoms?

- ☐ Fever of 100.4°F (38°C) or higher within the past 24 hours
- ☐ Cough

☐ **YES** ☐ **NO**

If you checked the NO box, **go to page 11.**

If you checked the YES box, **go to pages 12 and 13.**

Taking Steps to Feel Better

Treat symptoms with nonprescription medicines and/or take other steps to feel better.

Make sure the person rests and drinks plenty of fluids. Follow the directions on the product label if nonprescription medicines are taken.

Watch the person to see if symptoms get worse over the next 48 hours:

- **If cough AND fever of 100.4°F (38°C) or higher develops**, follow the instructions on page 12
- **Contact a doctor or seek medical care at the Emergency Room** if the person shows ANY of these signs:
  - — Continued fever after 48 hours of treatment with nonprescription medicines
  - — Severe vomiting (throwing up) or signs of dehydration (sunken eyes, leathery skin, dizziness when sitting up or standing, infrequent or dark urine)
  - — Worsening of or inability to care for an existing health condition (diabetes, asthma, etc)
- **Call 911 or take the person to the nearest Emergency Room** if you think that medical care is needed, or if the person has signs of severe illness. The person could have a serious health condition that is not caused by the flu

RELENZA®
(ZANAMIVIR) INHALATION POWDER

In the Event of Pandemic Flu, When Should I Take RELENZA for Treatment ?

Take RELENZA for TREATMENT if Pandemic Flu Is Announced in Your Area, and You...

HAVE HAD FLU SYMPTOMS FOR FEWER THAN 2 DAYS

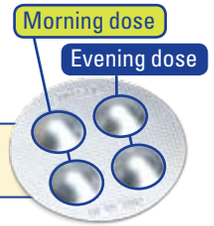
AND

ARE AT LEAST 7 YEARS OF AGE

TREATMENT =

INHALE 2 TIMES IN MORNING
AND
2 TIMES IN EVENING

REPEAT FOR 5 DAYS



Remember: Inhale 2 times (this means using 2 blisters) for 1 dose.

Please see Important Safety Information on page 18.
Children who use RELENZA should always be supervised by an adult who understands how to use RELENZA.

In the Event of Pandemic Flu, When Should I Take RELENZA for Prevention?

Take RELENZA for PREVENTION if Pandemic Flu Is Announced in Your Area, and You...

HAVE BEEN IN CLOSE CONTACT WITH A HOUSEHOLD MEMBER WHO HAS HAD THE FLU FOR FEWER THAN 2 DAYS

AND

ARE AT LEAST 5 YEARS OF AGE

PREVENTION =

INHALE 2 TIMES
ONCE A DAY

REPEAT FOR 10 DAYS

Remember: Inhale 2 times (this means using 2 blisters) for 1 dose.

Please see Important Safety Information on page 18.
Children who use RELENZA should always be supervised by an adult who understands how to use RELENZA.

RELENZA®
(ZANAMIVIR) INHALATION POWDER

When to Contact Your Doctor and/or Stop Taking RELENZA

Contact Your Doctor Before Using RELENZA if:

- Your health condition has changed, or you have developed a chronic condition such as heart or lung disease since the RELENZA MedKit was prescribed

Stop Using RELENZA and Call Your Doctor if You Develop Symptoms Such as:

- Wheezing or shortness of breath
- Rash or allergic reaction

Who Should Not Take RELENZA?

- People who have chronic lung disease such as asthma, chronic bronchitis, or emphysema. RELENZA may have serious side effects of severe breathing problems
- People who are allergic to RELENZA or lactose
- Children under 7 years of age should not use RELENZA for treatment
- Children under 5 years of age should not use RELENZA for prevention

This list of side effects is not complete. Your doctor or pharmacist can discuss with you a more complete list of possible side effects with RELENZA.

Talk to your doctor promptly about any side effects you have.

Seek Medical Care if You Don't Get Better

You should start feeling better in the first few days after you start taking RELENZA. If you don't get better when you are taking RELENZA, you should seek medical attention.

- **Call 911 or take the person to the nearest Emergency Room** if the signs of severe illness appear (see page 7)
- **Contact a doctor or seek medical care at the Emergency Room** if the person shows ANY of these signs:
  - Continued fever after 48 hours of treatment with nonprescription medicines
  - Severe vomiting (throwing up) or signs of dehydration (sunken eyes, leathery skin, dizziness when sitting up or standing, infrequent or dark urine)
  - Worsening of or inability to care for an existing health condition (diabetes, asthma, etc)
- While taking RELENZA seek medical care if you experience seizures, confusion, or abnormal behavior early in your illness

If you don't get better, it is possible that you do not have the flu and need to be treated for another illness. Or, you may have a type of flu that cannot be treated by medicine. Only a medical professional can tell you.

RELENZA®
(ZANAMIVIR) INHALATION POWDER

How Do I Use My RELENZA DISKHALER®?

PRACTICE: First, make sure you practice with the Practice-DISKHALER and Practice-ROTADISK®s. There is no drug in the Practice-ROTADISKs (contain air-filled blisters and do not contain real drug). The Practice-DISKHALER allows you to become familiar with the device and how to use it in preparation for actual use in the event of pandemic flu.

Practice-DISKHALER and Practice-ROTADISK (blister disk found in white canister).

RELENZA DISKHALER is in a small box marked RELENZA.

Your DISKHALER

Cover: blue; keeps DISKHALER clean

Mouthpiece: white; where medicine is inhaled

Needle: gray; punctures blister disk to release medicine

DISKHALER body: gray

Flap: gray; half circle lifts up and down to use needle

Tray: white; pulls in and out

Wheel: dark brown; rotates blister disk

Raised ridges: white; underneath the dark-brown wheel, squeeze to pull out tray

Blister disk: silver (found in white canister); holds medicine inside 4 blisters

For a video demonstration, go to **www.relenza.com**.

Children who use RELENZA should always be supervised by an adult who understands how to use RELENZA.

Just Think "Load...Puncture...Inhale"

LOAD

1 Remove blue cover.

2 Extend mouthpiece.

3 Remove white tray by pinching raised ridges below dark-brown wheel.

4 Load silver blister disk (found in white canister) into wheel (blister-side down) and insert white tray back into DISKHALER body.

PUNCTURE

5 Lift flap all the way to puncture blister. Medicine is a powder. Keep DISKHALER level for following steps.

6 Click flap back in place.

Read the Important Instructions section of the instruction sheet before using RELENZA.

INHALE

7 Breathe out without DISKHALER. Then deeply inhale medicine through mouthpiece.

8 Extend white tray. Close tray to rotate to new blister.

5 → 6 → 7 → 8

9 Repeat steps 5 to 8 **(you must inhale 2 times [this means using 2 blisters] for 1 full dose).**

RELENZA®
(ZANAMIVIR) INHALATION POWDER

Important Safety Information About RELENZA® (zanamivir) Inhalation Powder

Some people have had bronchospasm (wheezing) or serious breathing problems when they used RELENZA. Many but not all of these people had previous asthma or chronic obstructive pulmonary disease (COPD). Because of the risk of side effects, RELENZA is not best for people with chronic lung disease such as asthma or COPD.

If you develop symptoms such as wheezing or shortness of breath, stop using RELENZA and contact your doctor right away.

Other kinds of infections can appear like influenza or occur along with influenza, and need different kinds of treatment. Contact your doctor if you feel worse or develop new symptoms during or after treatment, or if your flu symptoms do not start to get better.

In studies, the most common side effects with RELENZA have been headaches; diarrhea; nausea; vomiting; nasal irritation; bronchitis; cough; sinusitis; ear, nose, and throat infections; and dizziness. Other side effects that have been reported, but were not as common, include rashes and allergic reactions, some of which were severe. If you develop a rash or have an allergic reaction, stop using RELENZA and contact your doctor.

People with influenza may be at increased risk of seizures, confusion, or abnormal behavior early in their illness. Therefore, patients should be observed for signs of unusual behavior, and a doctor contacted if needed.

This list of side effects is not complete. Your doctor or pharmacist can discuss with you a more complete list of possible side effects with RELENZA.

FAQs

Can I Share My RELENZA?

Never share RELENZA with anyone, even if they have the same symptoms. Only the person who got this drug from his/her doctor should use it.

What if I Miss a Dose?

If you forget to take your medicine at any time, take the missed dose as soon as you remember, except if it is near the next dose (within 2 hours). Then continue to take RELENZA at the usual times. If you have missed several doses, tell your doctor.

Can I Use RELENZA as a Substitute for Annual Flu Vaccine?

No. RELENZA is not a substitute for an annual flu vaccine.

What if My RELENZA DISKHALER® Breaks?

If the actual RELENZA DISKHALER in the box breaks, you can use your Practice-DISKHALER in the event of a pandemic.

What if My Practice-DISKHALER Breaks?

If your Practice-DISKHALER breaks, do NOT open the actual RELENZA DISKHALER. You need that for a pandemic. Contact your doctor.

What if Powder Gets Wet or Blows Away?

That's okay. Rotate the blister disk to a new, unopened blister.

What if I Cannot Taste/Feel Powder When I Breathe In?

That's okay. Not everyone can taste the medicine in RELENZA. Some may notice a sweet, lactose taste. Double-check the open blister to see if any medicine is left.

For more information, visit **www.relenza.com**.

RELENZA®
(ZANAMIVIR) INHALATION POWDER

For More Information on Pandemic Flu and RELENZA

Visit these Web sites:

US government official pandemic Web site—

www.pandemicflu.gov

World Health Organization (WHO) alert system—

www.who.int/csr/disease/avian_influenza/phase/en/index.html

Web site for RELENZA—

www.relenza.com

For questions or additional RELENZA information, call 1-800-[to come].

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

GlaxoSmithKline

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RELENZA®
(ZANAMIVIR) INHALATION POWDER

Diskhaler Instruction Sheet

Important Safety Information About RELENZA

Some people have had bronchospasm (wheezing) or serious breathing problems when they used RELENZA® (zanamivir) Inhalation Powder. Many but not all of these people had previous asthma or chronic obstructive pulmonary disease (COPD). Because of the risk of side effects, RELENZA is not best for people with chronic lung disease such as asthma or COPD.

If you develop symptoms such as wheezing or shortness of breath, stop using RELENZA and contact your doctor right away.

Other kinds of infections can appear like influenza or occur along with influenza, and need different kinds of treatment. Contact your doctor if you feel worse or develop new symptoms during or after treatment, or if your flu symptoms do not start to get better.

In studies, the most common side effects with RELENZA have been headaches; diarrhea; nausea; vomiting; nasal irritation; bronchitis; cough; sinusitis; ear, nose, and throat infections; and dizziness. Other side effects that have been reported, but were not as common, include rashes and allergic reactions, some of which were severe. If you develop a rash or have an allergic reaction, stop using RELENZA and contact your doctor.

People with influenza may be at increased risk of seizures, confusion, or abnormal behavior early in their illness. Therefore, patients should be observed for signs of unusual behavior, and a doctor contacted if needed.

This list of side effects is not complete. Your doctor or pharmacist can discuss with you a more complete list of possible side effects with RELENZA.

Talk to your doctor promptly about any side effects you have.

PANDEMIC FLU READINESS KIT

RELENZA® (ZANAMIVIR) INHALATION POWDER MED KIT™

DISKHALER® Instruction Sheet

GlaxoSmithKline

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TREATMENT

Pandemic Flu Is in Your Area and You…

HAVE HAD FLU SYMPTOMS FOR FEWER THAN 2 DAYS*

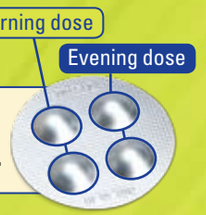
AND

ARE AT LEAST 7 YEARS OF AGE

TREATMENT =

INHALE 2 TIMES IN MORNING
AND
2 TIMES IN EVENING

REPEAT FOR 5 DAYS



Remember: Inhale 2 times (this means using 2 blisters) for 1 dose.

PREVENTION

Pandemic Flu Is in Your Area and You…

HAVE BEEN IN CONTACT WITH SOMEONE ILL WITH THE FLU WITHIN THE LAST 2 DAYS

AND

ARE AT LEAST 5 YEARS OF AGE

PREVENTION =

INHALE 2 TIMES
ONCE A DAY

REPEAT FOR 10 DAYS

Remember: Inhale 2 times (this means using 2 blisters) for 1 dose.

*Typical flu symptoms are listed on page 7 of the *Pandemic Flu Readiness Kit* Quick Guide.

Important Instructions

Read this entire leaflet before using RELENZA. Even if you have had a previous prescription for RELENZA, read this leaflet to see if any information has changed.

- For treatment of flu, inhale 2 times twice a day. For prevention of flu, inhale 2 times once a day
- Keep out of reach of children
- Always check inside the mouthpiece to make sure it is clear before each use. If foreign objects are in the mouthpiece, they could be inhaled and cause serious harm
- Always replace the cover after each use
- Throw away the DISKHALER® after treatment is completed
- This DISKHALER is for use only with RELENZA. Do not use the RELENZA DISKHALER device with FLOVENT® (fluticasone propionate) and do not use RELENZA with the FLOVENT DISKHALER device
- Children who use RELENZA should always be supervised by an adult who understands how to use RELENZA

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) (see USP Controlled Room Temperature).

REMEMBER: This medicine has been prescribed for you by your health care provider.

DO NOT give this medicine to anyone else.

Flovent is a registered trademark of GlaxoSmithKline.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

RELENZA®
(ZANAMIVIR) INHALATION POWDER

RELENZA DISKHALER® INSTRUCTION SHEET

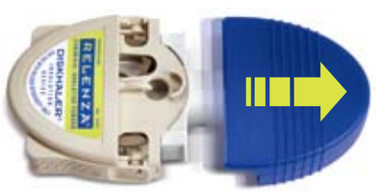
RELENZA®
(ZANAMIVIR) INHALATION POWDER

PRACTICE: First, make sure you practice with the Practice-DISKHALER and Practice-ROTADISK®s. There is no drug in the Practice-ROTADISKs (contain air-filled blisters and do not contain real drug). The Practice-DISKHALER allows you to become familiar with the device and how to use it in preparation for actual use in the event of pandemic flu.

Practice-DISKHALER and Practice-ROTADISK (blister disk found in white canister).

RELENZA DISKHALER is in a small box marked RELENZA.

LOAD



1 Remove blue cover.

2 Extend mouthpiece.

3 Remove white tray by pinching raised ridges below dark-brown wheel.

4 Load silver blister disk (found in white canister) into wheel (blister-side down) and insert white tray back into DISKHALER body.

PUNCTURE

5 Lift flap all the way to puncture blister. Medicine is a powder. Keep DISKHALER level for following steps.

6 Click flap back in place.

INHALE

7 Breathe out without DISKHALER. Then deeply inhale medicine through mouthpiece.

8 Extend white tray. Close tray to rotate to new blister.

Parts of the DISKHALER

For a video demonstration, go to **www.relenza.com.**

5 → 6 → 7 → 8

9 Repeat steps 5 to 8 (you must inhale 2 times [this means using 2 blisters] for 1 full dose).

Please see Important Safety Information on back.

APPENDIX 2: DRUG PRODUCTS HELD BY PATIENTS FOR USE OUTSIDE OF A USUAL CLINICAL SETTING

Following is a list of drug products (Rx or OTC) that are held by a patient or patient's family at home or work place (i.e., outside of a pharmacy, clinic, or hospital), where the product is intended for use by the patient or a family member or other person, outside of a usual clinic or doctor's office. These examples do not represent exact precedents for the scenario of home stockpiling of neuraminidase inhibitors for pandemic influenza, but they are provided here as informative examples. Most of these products are used as antidotes, or emergency care products that must be readily available for patient care.

Cyanokit was approved on December 15, 2006. It is an injectable product that comes in a pre-packed kit for the treatment of known or suspected cyanide poisoning. It is supplied in a carton that can be held in a workplace (e.g., chemical manufacturing facility) where cyanide is a hazard.

Pyridostigmine bromide tablets have been approved by FDA, mainly to be held and later used by soldiers before they could be exposed to the nerve agent, Soman. The product has explicit labeling that it is "for military use only".

ATNAA Injection was approved by FDA on January 17, 2002. It is combination of atropine and pralidoxime, used as an antidote for organophosphate poisoning. The NDA is held by the US Army and the product is used by military personnel. The labeling and FDA's review are posted to FDA's web site. The labeling includes detailed patient-directed instructions about how to properly use the product.

Epipen was approved by FDA on December 22, 1987. It is a widely used product, with which many healthcare professionals have experience. It is an auto-injector of epinephrine that is used for patient self-care in emergency situations due to an allergic reaction. It is supplied in a carton with instructions and everything needed to use the product. The manufacturer supplies practice syringes, separately to Healthcare Professionals, but not as part of the trade pack.

Diastat is a rectal gel formulation of diazepam. It was approved by FDA in 1997. It can be used in situations where a patient has certain refractory seizures that require treatment at home or in a care facility without a doctor immediately available. The product is usually administered by a nurse or family member. It has quite extensive labeling, including photos/illustrations, on how to use the product. The carton is self-contained and has everything needed (including packets of lubricating jelly) to use the product at home.

APPENDIX 3. SUMMARY OF REVIEW OF NEUROPSYCHIATRIC EVENTS REPORTED WITH ZANAMIVIR - OCTOBER 2007

This review of neuropsychiatric events and Relenza (zanamivir) was conducted in October 2007, following investigations that began when these events were first reported in Japan. Analyses include an integrated safety summary of Central Nervous System adverse events with zanamivir based on specifications from FDA. The current analysis was aimed at detecting risks for voluntary and involuntary self harm behaviors with the information provided in the adverse events reports available on the GSK Global Safety Database and at assessing if there was a potential causal association between CNS events and zanamivir.

No indication of a potential neuropsychiatric issue with zanamivir was observed through GSK's routine signal detection process until March 2007, at which time a cluster of such events observed in subjects exposed to zanamivir was reported to GSK from Japan. Almost all cases were in children or adolescents. It was apparent that the characteristics of the populations and the pattern of adverse events reported in the spring of 2007 differed significantly from the pattern observed in previous years, and therefore the data were presented separately for each of these two time periods.

Multiple sources of information were evaluated in this review, and the findings summarized below:

• In studies in animals there were no treatment related clinical signs indicative of effects on behavior. Penetration of zanamivir into the brain was shown to be minimal in radiolabel studies in rats and dogs.

• The pharmacokinetic characteristics of zanamivir make a direct CNS toxicity mechanism for neuropsychiatric events unlikely.

• A review of neuropsychiatric adverse events from all GSK Phase II and III centrally sponsored clinical trials (14,810 subjects enrolled, 8033 of whom received zanamivir) and studies conducted by GSK Japan (1049 subjects, 687 treated with zanamivir) was performed in November 2005. This review did not show an increased incidence of the neuropsychiatric events in subjects who received zanamivir compared with those who received placebo, or a comparator drug. The review was supplemented by an additional analysis of all the clinical trial Serious Adverse Event reports with zanamivir in which the current AE terms specified by FDA were used to search the GSK Worldwide Database. No evidence for a causal association with zanamivir was identified.

• Patterns of neuropsychiatric events or self harm behaviors have not been observed in three recent or ongoing Drug Use Investigations with zanamivir in Japan.

• Published epidemiology data describe that, although influenza is generally a self-limited illness, occasionally serious illness can occur with, among other manifestations, neurological involvement. Neurological involvement can be manifested as Reye's syndrome, acute necrotizing encephalopathy, myelitis, Guillain-Barre syndrome, encephalomyelitis and neuritis. Other observed symptoms include confusion, seizures,

and psychosis. In Japan, influenza associated encephalopathy is a frequently recognized serious complication of influenza, and the higher reporting of neuropsychiatric adverse events observed from Japan could be partly explained by this observation.

• There is no information available from the published medical and scientific literature linking use of zanamivir and neuropsychiatric events.

• A five fold increase in zanamivir use was observed in the past two years in Japan, which may contribute to the recently observed increase in spontaneous reporting of adverse events from this country.

• The peak of neuropsychiatric events reported in subjects exposed to zanamivir during March and April 2007 corresponded to the peak of a "widespread outbreak" of influenza like illnesses (ILI) in Japan [WHO influenza disease resource information]. In the USA, widespread outbreaks of ILI were described in December 2006 to January 07, as well as in February and March 2007. No reports of neuropsychiatric adverse events have been received from the USA.

• An association was noted between the reporting of neuropsychiatric events from Japan in subjects exposed to zanamivir in the spring of 2007 and the public release of a high level alert by the Japanese Ministry of Health, Labor and Welfare in March 2007 which detailed abnormal / self harm behaviors observed in Japanese adolescents infected with influenza and exposed to oseltamivir. Awareness of this alert was stated in many of these neuropsychiatric adverse events reports sent to GSK by Japanese reporters.

• In the Northern Hemisphere, influenza activity has been low during the past two influenza seasons. However, data from the Japanese government Infectious Disease Surveillance Center indicate that a slightly higher influenza activity was prevalent in Japan during 2006-7 in comparison with the rest of the northern hemisphere or with the Japanese 2005-6 influenza season. The high reporting of neuropsychiatric events in Japanese children and adolescents in the spring of 2007 may be due partially to a slightly higher influenza activity in Japan in March and April 2007. However, this increased reporting of adverse events in the spring of 2007 could also be due to the fact that this population was more likely than others to seek medical consultation when infected with influenza.

• All 145 reports of neuropsychiatric events received in the spring of 2007 were issued from Japan. Ninety two percent of cases were observed in children and adolescents younger than 18 years of age and 99% in children in the 6-14 age range. The vast majority of these events were transient and a significant proportion of the reports described abnormal behavior in febrile subjects that resolved while zanamivir treatment was continued. No falls or jumps from high places or suicides were reported.

• Neuropsychiatric adverse events reported prior to the 2006-2007 influenza season were significantly different in their origin, clinical presentation pattern and characteristics of the population affected than what was observed in the cluster of reports from Japan in the spring of 2007: the older reports were issued from multiple of countries, did not show a specific medical pattern, and the population affected was significantly older than the population typical of the reports from Japan in the spring of 2007.

APPENDIX 4. US PRESCRIBING INFORMATION

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use RELENZA safely and effectively. See full prescribing information for RELENZA.

RELENZA® (zanamivir) Inhalation Powder, for oral inhalation
Initial U.S. Approval: 1999

RECENT MAJOR CHANGES

Warnings and Precautions
Neuropsychiatric Events (5.3) February 2008

INDICATIONS AND USAGE

RELENZA, an influenza neuraminidase inhibitor, is indicated for:
Treatment of influenza in patients 7 years of age and older who have been symptomatic for no more than 2 days. (1.1)
Prophylaxis of influenza in patients 5 years of age and older. (1.2)

Important Limitations on Use of RELENZA:
Not recommended for treatment or prophylaxis of influenza in:

- Individuals with underlying airways disease. (5.1)

Not proven effective for:

- Treatment in individuals with underlying airways disease. (1.3)
- Prophylaxis in nursing home residents. (1.3)

Not a substitute for annual influenza vaccination. (1.3)

DOSAGE AND ADMINISTRATION

Indication	Dose
Treatment of Influenza (2.2)	10 mg twice daily for 5 days
Prophylaxis: (2.3)	
Household Setting	10 mg once daily for 10 days
Community Outbreaks	10 mg once daily for 28 days

Note: The 10 mg dose is provided by 2 inhalations (one 5 mg blister per inhalation). (2.1)

DOSAGE FORMS AND STRENGTHS

Four 5 mg blisters of powder on a ROTADISK® for oral inhalation via DISKHALER®. Packaged in carton containing 5 ROTADISKs (total of 10 doses) and 1 DISKHALER inhalation device. (3)

CONTRAINDICATIONS

Do not use in patients with history of allergic reaction to any ingredient of RELENZA, including lactose (which contains milk proteins). (4)

WARNINGS AND PRECAUTIONS

- **Bronchospasm:** Serious, sometimes fatal, cases have occurred. Not recommended in individuals with underlying airways disease. Discontinue RELENZA if bronchospasm or decline in respiratory function develops. (5.1)
- **Allergic Reactions:** Discontinue RELENZA and initiate appropriate treatment if an allergic reaction occurs or is suspected. (5.2)
- **Neuropsychiatric Events:** Patients with influenza, particularly pediatric patients, may be at an increased risk of seizures, confusion, or abnormal behavior early in their illness. Monitor for signs of abnormal behavior. (5.3)
- **High-risk underlying medical conditions:** Safety and effectiveness have not been demonstrated in these patients. (5.4)

ADVERSE REACTIONS

The most common adverse events reported in >1.5% of patients treated with RELENZA and more commonly than in patients treated with placebo are:

- Treatment Studies – sinusitis, dizziness.
- Prophylaxis studies – fever and/or chills, arthralgia and articular rheumatism. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Live attenuated influenza vaccine, intranasal (7):

- Do not administer until 48 hours following cessation of RELENZA.
- Do not administer RELENZA until 2 weeks following administration of the live attenuated influenza vaccine, unless medically indicated.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: February 2008
RLZ:3PI

FULL PRESCRIBING INFORMATION: CONTENTS*

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1.2 Prophylaxis of Influenza
1.3 Important Limitations on Use of RELENZA
2 DOSAGE AND ADMINISTRATION
2.1 Dosing Considerations
2.2 Treatment of Influenza
2.3 Prophylaxis of Influenza
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Bronchospasm
5.2 Allergic Reactions
5.3 Neuropsychiatric Events
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5.5 Bacterial Infections
5.6 Importance of Proper Use of DISKHALER
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12 CLINICAL PHARMACOLOGY
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17 PATIENT COUNSELING INFORMATION
17.1 Bronchospasm
17.2 Concomitant Bronchodilator Use
17.3 Neuropsychiatric Events
17.4 Instructions for Use
17.5 Risk of Influenza Transmission to Others
17.6 FDA-Approved Patient Labeling and Instructions for Use

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Treatment of Influenza

RELENZA is indicated for treatment of uncomplicated acute illness due to influenza A and B virus in adults and pediatric patients 7 years of age and older who have been symptomatic for no more than 2 days.

1.2 Prophylaxis of Influenza

RELENZA is indicated for prophylaxis of influenza in adults and pediatric patients 5 years of age and older.

1.3 Important Limitations on Use of RELENZA

- RELENZA is not recommended for treatment or prophylaxis of influenza in individuals with underlying airways disease (such as asthma or chronic obstructive pulmonary disease) due to risk of serious bronchospasm *[see Warnings and Precautions (5.1)]*.
- RELENZA has not been proven effective for treatment of influenza in individuals with underlying airways disease.
- RELENZA has not been proven effective for prophylaxis of influenza in the nursing home setting.
- RELENZA is not a substitute for early influenza vaccination on an annual basis as recommended by the Centers for Disease Control's Immunization Practices Advisory Committee.
- There is no evidence for efficacy of zanamivir in any illness caused by agents other than influenza virus A and B.
- Patients should be advised that the use of RELENZA for treatment of influenza has not been shown to reduce the risk of transmission of influenza to others.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Considerations

- RELENZA is for administration to the respiratory tract by oral inhalation only, using the DISKHALER device provided.
- The 10 mg dose is provided by 2 inhalations (one 5 mg blister per inhalation).
- Patients should be instructed in the use of the delivery system. Instructions should include a demonstration whenever possible. If RELENZA is prescribed for children, it should be used only under adult supervision and instruction, and the supervising adult should first be instructed by a healthcare professional *[see Patient Counseling Information (17.4)]*.
- Patients scheduled to use an inhaled bronchodilator at the same time as RELENZA should use their bronchodilator before taking RELENZA *[see Patient Counseling Information (17.2)]*.

2.2 Treatment of Influenza

- The recommended dose of RELENZA for treatment of influenza in adults and pediatric patients ages 7 years of age and older is 10 mg twice daily (approximately 12 hours apart) for 5 days.
- Two doses should be taken on the first day of treatment whenever possible provided there is at least 2 hours between doses.
- On subsequent days, doses should be about 12 hours apart (e.g., morning and evening) at approximately the same time each day.
- The safety and efficacy of repeated treatment courses have not been studied.

2.3 Prophylaxis of Influenza

Household Setting:

- The recommended dose of RELENZA for prophylaxis of influenza in adults and pediatric patients 5 years of age and older in a household setting is 10 mg once daily for 10 days.
- The dose should be administered at approximately the same time each day.
- There are no data on the effectiveness of prophylaxis with RELENZA in a household setting when initiated more than 1.5 days after the onset of signs or symptoms in the index case.

Community Outbreaks:

- The recommended dose of RELENZA for prophylaxis of influenza in adults and adolescents in a community setting is 10 mg once daily for 28 days.
- The dose should be administered at approximately the same time each day.
- There are no data on the effectiveness of prophylaxis with RELENZA in a community outbreak when initiated more than 5 days after the outbreak was identified in the community.
- The safety and effectiveness of prophylaxis with RELENZA have not been evaluated for longer than 28 days' duration.

3 DOSAGE FORMS AND STRENGTHS

Four 5 mg blisters of powder on a ROTADISK for oral inhalation via DISKHALER. Packaged in carton containing 5 ROTADISKs (total of 10 doses) and 1 DISKHALER inhalation device *[see How Supplied/Storage and Handling (16)]*.

4 CONTRAINDICATIONS

Do not use in patients with history of allergic reaction to any ingredient of RELENZA including lactose (which contains milk proteins) *[see Warnings and Precautions (5.2), Description (11)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Bronchospasm

RELENZA is not recommended for treatment or prophylaxis of influenza in individuals with underlying airways disease (such as asthma or chronic obstructive pulmonary disease).

Serious cases of bronchospasm, including fatalities, have been reported during treatment with RELENZA in patients with and without underlying airways disease. Many of these cases were reported during postmarketing and causality was difficult to assess.

RELENZA should be discontinued in any patient who develops bronchospasm or decline in respiratory function; immediate treatment and hospitalization may be required.

Some patients without prior pulmonary disease may also have respiratory abnormalities from acute respiratory infection that could resemble adverse drug reactions or increase patient vulnerability to adverse drug reactions.

Bronchospasm was documented following administration of zanamivir in 1 of 13 patients with mild or moderate asthma (but without acute influenza-like illness) in a Phase I study. In a Phase III study in patients with acute influenza-like illness superimposed on underlying asthma or chronic obstructive pulmonary disease, 10% (24 of 244) of patients on zanamivir and 9% (22 of 237) on placebo experienced a greater than 20% decline in FEV_1 following treatment for 5 days.

If use of RELENZA is considered for a patient with underlying airways disease, the potential risks and benefits should be carefully weighed. If a decision is made to prescribe RELENZA for such a patient, this should be done only under conditions of careful monitoring of respiratory function, close observation, and appropriate supportive care including availability of fast-acting bronchodilators.

5.2 Allergic Reactions

Allergic-like reactions, including oropharyngeal edema, serious skin rashes, and anaphylaxis have been reported in postmarketing experience with RELENZA. RELENZA should be stopped and appropriate treatment instituted if an allergic reaction occurs or is suspected.

5.3 Neuropsychiatric Events

Influenza can be associated with a variety of neurologic and behavioral symptoms which can include events such as seizures, hallucinations, delirium, and abnormal behavior, in some cases resulting in fatal outcomes. These events may occur in the setting of encephalitis or encephalopathy but can occur without obvious severe disease.

There have been postmarketing reports (mostly from Japan) of delirium and abnormal behavior leading to injury in patients with influenza who were receiving neuraminidase inhibitors, including RELENZA. Because these events were reported voluntarily during clinical practice, estimates of frequency cannot be made, but they appear to be uncommon based on usage data for RELENZA. These events were reported primarily among pediatric patients and often had an abrupt onset and rapid resolution. The contribution of RELENZA to these events has not been established. Patients with influenza should be closely monitored for signs of abnormal behavior. If neuropsychiatric symptoms occur, the risks and benefits of continuing treatment should be evaluated for each patient.

5.4 Limitations of Populations Studied

Safety and efficacy have not been demonstrated in patients with high-risk underlying medical conditions. 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.

5.5 Bacterial Infections

Serious bacterial infections may begin with influenza-like symptoms or may coexist with or occur as complications during the course of influenza. RELENZA has not been shown to prevent such complications.

5.6 Importance of Proper Use of DISKHALER

Effective and safe use of RELENZA requires proper use of the DISKHALER to inhale the drug. Prescribers should carefully evaluate the ability of young children to use the delivery system if use of RELENZA is considered *[see Use in Specific Populations (8.4)]*.

6 ADVERSE REACTIONS

See Warnings and Precautions for information about risk of serious adverse events such as bronchospasm (5.1) and allergic-like reactions (5.2), and for safety information in patients with underlying airways disease (5.1).

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The placebo used in clinical studies consisted of inhaled lactose powder, which is also the vehicle for the active drug; therefore, some adverse events occurring at similar frequencies in different treatment groups could be related to lactose vehicle inhalation.

Treatment of Influenza: *Clinical Trials in Adults and Adolescents:* Adverse events that occurred with an incidence ≥1.5% in treatment studies are listed in Table 1. This table shows adverse events occurring in patients ≥12 years of age receiving RELENZA 10 mg inhaled twice daily, RELENZA in all inhalation regimens, and placebo inhaled twice daily (where placebo consisted of the same lactose vehicle used in RELENZA).

Table 1. Summary of Adverse Events ≥1.5% Incidence During Treatment in Adults and Adolescents

Adverse Event	RELENZA 10 mg b.i.d. **Inhaled** (n = 1,132)	RELENZA All Dosing Regimens* (n = 2,289)	Placebo (Lactose Vehicle) (n = 1,520)
Body as a whole			
Headaches	2%	2%	3%
Digestive			
Diarrhea	3%	3%	4%
Nausea	3%	3%	3%
Vomiting	1%	1%	2%
Respiratory			
Nasal signs and symptoms	2%	3%	3%
Bronchitis	2%	2%	3%
Cough	2%	2%	3%
Sinusitis	3%	2%	2%
Ear, nose, and throat infections	2%	1%	2%
Nervous system			
Dizziness	2%	1%	<1%

* Includes studies where RELENZA was administered intranasally (6.4 mg 2 to 4 times per day in addition to inhaled preparation) and/or inhaled more frequently (q.i.d.) than the currently recommended dose.

Additional adverse reactions occurring in less than 1.5% of patients receiving RELENZA included malaise, fatigue, fever, abdominal pain, myalgia, arthralgia, and urticaria.

The most frequent laboratory abnormalities in Phase III treatment studies included elevations of liver enzymes and CPK, lymphopenia, and neutropenia. These were reported in similar proportions of zanamivir and lactose vehicle placebo recipients with acute influenza-like illness.

Clinical Trials in Pediatric Patients: Adverse events that occurred with an incidence ≥1.5% in children receiving treatment doses of RELENZA in 2 Phase III studies are listed in Table 2. This table shows adverse events occurring in pediatric patients 5 to 12 years old receiving RELENZA 10 mg inhaled twice daily and placebo inhaled twice daily (where placebo consisted of the same lactose vehicle used in RELENZA).

Table 2. Summary of Adverse Events ≥1.5% Incidence During Treatment in Pediatric Patients*

Adverse Event	RELENZA 10 mg b.i.d. Inhaled (n = 291)	Placebo (Lactose Vehicle) (n = 318)
Respiratory		
Ear, nose, and throat infections	5%	5%
Ear, nose, and throat hemorrhage	<1%	2%
Asthma	<1%	2%
Cough	<1%	2%
Digestive		
Vomiting	2%	3%
Diarrhea	2%	2%
Nausea	<1%	2%

* Includes a subset of patients receiving RELENZA for treatment of influenza in a prophylaxis study.

In 1 of the 2 studies described in Table 2, some additional information is available from children (5 to 12 years old) without acute influenza-like illness who received an investigational prophylaxis regimen of RELENZA; 132 children received RELENZA and 145 children received placebo. Among these children, nasal signs and symptoms (zanamivir 20%, placebo 9%), cough (zanamivir 16%, placebo 8%), and throat/tonsil discomfort and pain (zanamivir 11%, placebo 6%) were reported more frequently with RELENZA than placebo. In a subset with chronic pulmonary disease, lower respiratory adverse events (described as asthma, cough, or viral respiratory infections which could include influenza-like symptoms) were reported in 7 of 7 zanamivir recipients and 5 of 12 placebo recipients.

Prophylaxis of Influenza: *Family/Household Prophylaxis Studies:* Adverse events that occurred with an incidence of ≥1.5% in the 2 prophylaxis studies are listed in Table 3. This table shows adverse events occurring in patients ≥5 years of age receiving RELENZA 10 mg inhaled once daily for 10 days.

Table 3. Summary of Adverse Events ≥1.5% Incidence During 10-Day Prophylaxis Studies in Adults, Adolescents, and Children*

Adverse Event	Contact Cases	
	RELENZA (n = 1,068)	Placebo (n = 1,059)
Lower respiratory		
Viral respiratory infections	13%	19%
Cough	7%	9%
Neurologic		
Headaches	13%	14%
Ear, nose, and throat		
Nasal signs and symptoms	12%	12%
Throat and tonsil discomfort and pain	8%	9%
Nasal inflammation	1%	2%
Musculoskeletal		
Muscle pain	3%	3%
Endocrine and metabolic		
Feeding problems (decreased or increased appetite and anorexia)	2%	2%
Gastrointestinal		
Nausea and vomiting	1%	2%
Non-site specific		
Malaise and fatigue	5%	5%
Temperature regulation disturbances (fever and/or chills)	5%	4%

* In prophylaxis studies, symptoms associated with influenza-like illness were captured as adverse events; subjects were enrolled during a winter respiratory season during which time any symptoms that occurred were captured as adverse events.

Community Prophylaxis Studies: Adverse events that occurred with an incidence of ≥1.5% in 2 prophylaxis studies are listed in Table 4. This table shows adverse events occurring in patients ≥5 years of age receiving RELENZA 10 mg inhaled once daily for 28 days.

Table 4. Summary of Adverse Events ≥1.5% Incidence During 28-Day Prophylaxis Studies in Adults, Adolescents, and Children*

Adverse Event	RELENZA (n = 2,231)	Placebo (n = 2,239)
Neurologic		
Headaches	24%	26%
Ear, nose, and throat		
Throat and tonsil discomfort and pain	19%	20%
Nasal signs and symptoms	12%	13%
Ear, nose, and throat infections	2%	2%
Lower respiratory		
Cough	17%	18%
Viral respiratory infections	3%	4%
Musculoskeletal		
Muscle pain	8%	8%
Musculoskeletal pain	6%	6%
Arthralgia and articular rheumatism	2%	<1%
Endocrine and metabolic		
Feeding problems (decreased or increased appetite and anorexia)	4%	4%
Gastrointestinal		
Nausea and vomiting	2%	3%
Diarrhea	2%	2%
Non-site specific		
Temperature regulation disturbances (fever and/or chills)	9%	10%
Malaise & fatigue	8%	8%

* In prophylaxis studies, symptoms associated with influenza-like illness were captured as adverse events; subjects were enrolled during a winter respiratory season during which time any symptoms that occurred were captured as adverse events.

6.2 Postmarketing Experience

In addition to adverse events reported from clinical trials, the following events have been identified during postmarketing use of zanamivir (RELENZA). Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to zanamivir (RELENZA).

Allergic Reactions: Allergic or allergic-like reaction, including oropharyngeal edema *[see Warnings and Precautions (5.2)]*.

Psychiatric: Delirium, including symptoms such as altered level of consciousness, confusion, abnormal behavior, delusions, hallucinations, agitation, anxiety, nightmares *[see Warnings and Precautions (5.3)]*.

Cardiac: Arrhythmias, syncope.

Neurologic: Seizures.

Respiratory: Bronchospasm, dyspnea *[see Warnings and Precautions (5.1)]*.

Skin: Facial edema; rash, including serious cutaneous reactions; urticaria *[see Warnings and Precautions (5.2)]*.

7 DRUG INTERACTIONS

Zanamivir is not a substrate nor does it affect cytochrome P450 (CYP) isoenzymes (CYP1A1/2, 2A6, 2C9, 2C18, 2D6, 2E1, and 3A4) in human liver microsomes. No clinically significant pharmacokinetic drug interactions are predicted based on data from in vitro studies.

The concurrent use of RELENZA with live attenuated influenza vaccine (LAIV) intranasal has not been evaluated. However, because of potential interference between these products, LAIV should not be administered within 2 weeks before or 48 hours after administration of RELENZA, unless medically indicated. The concern about possible interference arises from the potential for antiviral drugs to inhibit replication of live vaccine virus.

Trivalent inactivated influenza vaccine can be administered at any time relative to use of RELENZA *[see Clinical Pharmacology (12.4)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. There are no adequate and well-controlled studies of zanamivir in pregnant women. Zanamivir should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Embryo/fetal development studies were conducted in rats (dosed from days 6 to 15 of pregnancy) and rabbits (dosed from days 7 to 19 of pregnancy) using the same IV doses (1, 9, and 90 mg/kg/day). Pre- and post-natal developmental studies were performed in rats (dosed from day 16 of pregnancy until litter day 21 to 23). No malformations, maternal toxicity, or embryotoxicity were observed in pregnant rats or rabbits and their fetuses. Because of insufficient blood sampling timepoints in rat and rabbit reproductive toxicity studies, AUC values were not available. In a subchronic study in rats at the 90 mg/kg/day IV dose, the AUC values were greater than 300 times the human exposure at the proposed clinical dose.

An additional embryo/fetal study, in a different strain of rat, was conducted using subcutaneous administration of zanamivir, 3 times daily, at doses of 1, 9, or 80 mg/kg during days 7 to 17 of pregnancy. There was an increase in the incidence rates of a variety of minor skeleton alterations and variants in the exposed offspring in this study. Based on AUC measurements, the 80 mg/kg dose produced an exposure greater than 1,000 times the human exposure at the proposed clinical dose. However, in most instances, the individual incidence rate

of each skeletal alteration or variant remained within the background rates of the historical occurrence in the strain studied.

Zanamivir has been shown to cross the placenta in rats and rabbits. In these animals, fetal blood concentrations of zanamivir were significantly lower than zanamivir concentrations in the maternal blood.

8.3 Nursing Mothers

Studies in rats have demonstrated that zanamivir is excreted in milk. However, nursing mothers should be instructed that it is not known whether zanamivir is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when RELENZA is administered to a nursing mother.

8.4 Pediatric Use

Treatment of Influenza: Safety and effectiveness of RELENZA for treatment of influenza have not been assessed in pediatric patients less than 7 years of age, but were studied in a Phase III treatment study in pediatric patients, where 471 children 5 to 12 years of age received zanamivir or placebo *[see Clinical Studies 14.1)]*. Adolescents were included in the three principal Phase III adult treatment studies. In these studies, 67 patients were 12 to 16 years of age. No definite differences in safety and efficacy were observed between these adolescent patients and young adults.

In a Phase I study of 16 children ages 6 to 12 years with signs and symptoms of respiratory disease, 4 did not produce a measurable peak inspiratory flow rate (PIFR) through the DISKHALER (3 with no adequate inhalation on request, 1 with missing data), 9 had measurable PIFR on each of 2 inhalations, and 3 achieved measurable PIFR on only 1 of 2 inhalations. Neither of two 6-year-olds and one of two 7-year-olds produced measurable PIFR. Overall, 8 of the 16 children (including all those under 8 years old) either did not produce measurable inspiratory flow through the DISKHALER or produced peak inspiratory flow rates below the 60 L/min considered optimal for the device under standardized in vitro testing; lack of measurable flow rate was related to low or undetectable serum concentrations *[see Clinical Pharmacology (12.3), Clinical Studies (14.1)]*. Prescribers should carefully evaluate the ability of young children to use the delivery system if prescription of RELENZA is considered.

Prophylaxis of Influenza: The safety and effectiveness of RELENZA for prophylaxis of influenza have been studied in 4 Phase III studies where 273 children 5 to 11 years of age and 239 adolescents 12 to 16 years of age received RELENZA. No differences in safety and effectiveness were observed between pediatric and adult subjects *[see Clinical Studies (14.2)]*.

8.5 Geriatric Use

Of the total number of patients in 6 clinical studies of RELENZA for treatment of influenza, 59 patients were 65 years of age and older, while 24 patients were 75 years of age and older. Of the total number of patients in 4 clinical studies of RELENZA for prophylaxis of influenza in households and community settings, 954 patients were 65 years of age and older, while 347 patients were 75 years of age and older. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported

clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Elderly patients may need assistance with use of the device.

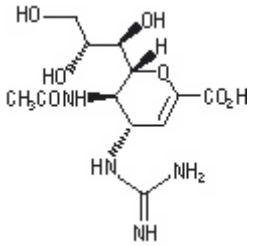
In 2 additional studies of RELENZA for prophylaxis of influenza in the nursing home setting, efficacy was not demonstrated *[see Indications and Usage (1.3)]*.

10 OVERDOSAGE

There have been no reports of overdosage from administration of RELENZA.

11 DESCRIPTION

The active component of RELENZA is zanamivir. The chemical name of zanamivir is 5-(acetylamino)-4-[(aminoiminomethyl)-amino]-2,6-anhydro-3,4,5-trideoxy-D-glycero-D-galacto-non-2-enonic acid. It has a molecular formula of $C_{12}H_{20}N_4O_7$ and a molecular weight of 332.3. It has the following structural formula:



Zanamivir is a white to off-white powder for oral inhalation with a solubility of approximately 18 mg/mL in water at 20°C.

RELENZA is for administration to the respiratory tract by oral inhalation only. Each RELENZA ROTADISK contains 4 regularly spaced double-foil blisters with each blister containing a powder mixture of 5 mg of zanamivir and 20 mg of lactose (which contains milk proteins). The contents of each blister are inhaled using a specially designed breath-activated plastic device for inhaling powder called the DISKHALER. After a RELENZA ROTADISK is loaded into the DISKHALER, a blister that contains medication is pierced and the zanamivir is dispersed into the air stream created when the patient inhales through the mouthpiece. The amount of drug delivered to the respiratory tract will depend on patient factors such as inspiratory flow. Under standardized in vitro testing, RELENZA ROTADISK delivers 4 mg of zanamivir from the DISKHALER device when tested at a pressure drop of 3 kPa (corresponding to a flow rate of about 62 to 65 L/min) for 3 seconds.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Zanamivir is an antiviral drug *[see Clinical Pharmacology (12.4)]*.

12.3 Pharmacokinetics

Absorption and Bioavailability: Pharmacokinetic studies of orally inhaled zanamivir indicate that approximately 4% to 17% of the inhaled dose is systemically absorbed. The peak

serum concentrations ranged from 17 to 142 ng/mL within 1 to 2 hours following a 10 mg dose. The area under the serum concentration versus time curve (AUC_∞) ranged from 111 to 1,364 ng•hr/mL.

Distribution: Zanamivir has limited plasma protein binding (<10%).

Metabolism: Zanamivir is renally excreted as unchanged drug. No metabolites have been detected in humans.

Elimination: The serum half-life of zanamivir following administration by oral inhalation ranges from 2.5 to 5.1 hours. It is excreted unchanged in the urine with excretion of a single dose completed within 24 hours. Total clearance ranges from 2.5 to 10.9 L/hr. Unabsorbed drug is excreted in the feces.

Impaired Hepatic Function: The pharmacokinetics of zanamivir have not been studied in patients with impaired hepatic function.

Impaired Renal Function: After a single intravenous dose of 4 mg or 2 mg of zanamivir in volunteers with mild/moderate or severe renal impairment, respectively, significant decreases in renal clearance (and hence total clearance: normals 5.3 L/hr, mild/moderate 2.7 L/hr, and severe 0.8 L/hr; median values) and significant increases in half-life (normals 3.1 hr, mild/moderate 4.7 hr, and severe 18.5 hr; median values) and systemic exposure were observed. Safety and efficacy have not been documented in the presence of severe renal insufficiency. Due to the low systemic bioavailability of zanamivir following oral inhalation, no dosage adjustments are necessary in patients with renal impairment. However, the potential for drug accumulation should be considered.

Pediatric Patients: The pharmacokinetics of zanamivir were evaluated in pediatric patients with signs and symptoms of respiratory illness. Sixteen patients, 6 to 12 years of age, received a single dose of 10 mg zanamivir dry powder via DISKHALER. Five patients had either undetectable zanamivir serum concentrations or had low drug concentrations (8.32 to 10.38 ng/mL) that were not detectable after 1.5 hours. Eleven patients had C_{max} median values of 43 ng/mL (range 15 to 74) and AUC_∞ median values of 167 ng•hr/mL (range 58 to 279). Low or undetectable serum concentrations were related to lack of measurable PIFR in individual patients *[see Use in Specific Populations (8.4), Clinical Studies (14.1)]*.

Geriatric Patients: The pharmacokinetics of zanamivir have not been studied in patients over 65 years of age *[see Use in Specific Populations (8.5)]*.

Gender, Race, and Weight: In a population pharmacokinetic analysis in patient studies, no clinically significant differences in serum concentrations and/or pharmacokinetic parameters (V/F, CL/F, ka, AUC_{0-3}, C_{max}, T_{max}, CLr, and % excreted in urine) were observed when demographic variables (gender, age, race, and weight) and indices of infection (laboratory evidence of infection, overall symptoms, symptoms of upper respiratory illness, and viral titers) were considered. There were no significant correlations between measures of systemic exposure and safety parameters.

12.4 Microbiology

Mechanism of Action: Zanamivir is an inhibitor of influenza virus neuraminidase affecting release of viral particles.

Antiviral Activity: The antiviral activity of zanamivir against laboratory and clinical isolates of influenza virus was determined in cell culture assays. The concentrations of zanamivir required for inhibition of influenza virus were highly variable depending on the assay method used and virus isolate tested. The 50% and 90% effective concentrations (EC_{50} and EC_{90}) of zanamivir were in the range of 0.005 to 16.0 μM and 0.05 to >100 μM, respectively (1 μM = 0.33 mcg/mL). The relationship between the cell culture inhibition of influenza virus by zanamivir and the inhibition of influenza virus replication in humans has not been established.

Resistance: Influenza viruses with reduced susceptibility to zanamivir have been selected in cell culture by multiple passages of the virus in the presence of increasing concentrations of the drug. Genetic analysis of these viruses showed that the reduced susceptibility in cell culture to zanamivir is associated with mutations that result in amino acid changes in the viral neuraminidase or viral hemagglutinin or both. Resistance mutations selected in cell culture which result in neuraminidase amino acid substitutions include E119G/A/D and R292K. Mutations selected in cell culture in hemagglutinin include: K68R, G75E, E114K, N145S, S165N, S186F, N199S, and K222T.

In an immunocompromised patient infected with influenza B virus, a variant virus emerged after treatment with an investigational nebulized solution of zanamivir for 2 weeks. Analysis of this variant showed a hemagglutinin substitution (T198I) which resulted in a reduced affinity for human cell receptors, and a substitution in the neuraminidase active site (R152K) which reduced the enzyme's activity to zanamivir by 1,000-fold. Insufficient information is available to characterize the risk of emergence of zanamivir resistance in clinical use.

Cross-Resistance: Cross-resistance has been observed between some zanamivir-resistant and some oseltamivir-resistant influenza virus mutants generated in cell culture. However, some of the in cell culture zanamivir-induced resistance mutations, E119G/A/D and R292K, occurred at the same neuraminidase amino acid positions as in the clinical isolates resistant to oseltamivir, E119V and R292K. No studies have been performed to assess risk of emergence of cross-resistance during clinical use.

Influenza Vaccine Interaction Study: An interaction study (n = 138) was conducted to evaluate the effects of zanamivir (10 mg once daily) on the serological response to a single dose of trivalent inactivated influenza vaccine, as measured by hemagglutination inhibition titers. There was no difference in hemagglutination inhibition antibody titers at 2 weeks and 4 weeks after vaccine administration between zanamivir and placebo recipients.

Influenza Challenge Studies: Antiviral activity of zanamivir was supported for infection with influenza A virus, and to a more limited extent for infection with influenza B virus, by Phase I studies in volunteers who received intranasal inoculations of challenge strains of influenza virus, and received an intranasal formulation of zanamivir or placebo starting before or shortly after viral inoculation.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: In 2-year carcinogenicity studies conducted in rats and mice using a powder formulation administered through inhalation, zanamivir induced no statistically significant increases in tumors over controls. The maximum daily exposures in rats and mice were approximately 23 to 25 and 20 to 22 times, respectively, greater than those in humans at the proposed clinical dose based on AUC comparisons.

Mutagenesis: Zanamivir was not mutagenic in in vitro and in vivo genotoxicity assays which included bacterial mutation assays in *S. typhimurium* and *E. coli*, mammalian mutation assays in mouse lymphoma, chromosomal aberration assays in human peripheral blood lymphocytes, and the in vivo mouse bone marrow micronucleus assay.

Impairment of Fertility: The effects of zanamivir on fertility and general reproductive performance were investigated in male (dosed for 10 weeks prior to mating, and throughout mating, gestation/lactation, and shortly after weaning) and female rats (dosed for 3 weeks prior to mating through Day 19 of pregnancy, or Day 21 post partum) at IV doses 1, 9, and 90 mg/kg/day. Zanamivir did not impair mating or fertility of male or female rats, and did not affect the sperm of treated male rats. The reproductive performance of the F1 generation born to female rats given zanamivir was not affected. Based on a subchronic study in rats at a 90 mg/kg/day IV dose, AUC values ranged between 142 and 199 mcg•hr/mL (>300 times the human exposure at the proposed clinical dose).

14 CLINICAL STUDIES

14.1 Treatment of Influenza

Adults and Adolescents: The efficacy of RELENZA 10 mg inhaled twice daily for 5 days in the treatment of influenza has been evaluated in placebo-controlled studies conducted in North America, the Southern Hemisphere, and Europe during their respective influenza seasons. The magnitude of treatment effect varied between studies, with possible relationships to population-related factors including amount of symptomatic relief medication used.

Populations Studied: The principal Phase III studies enrolled 1,588 patients ages 12 years and older (median age 34 years, 49% male, 91% Caucasian), with uncomplicated influenza-like illness within 2 days of symptom onset. Influenza was confirmed by culture, hemagglutination inhibition antibodies, or investigational direct tests. Of 1,164 patients with confirmed influenza, 89% had influenza A and 11% had influenza B. These studies served as the principal basis for efficacy evaluation, with more limited Phase II studies providing supporting information where necessary. Following randomization to either zanamivir or placebo (inhaled lactose vehicle), all patients received instruction and supervision by a healthcare professional for the initial dose.

Principal Results: The definition of time to improvement in major symptoms of influenza included no fever and self-assessment of “none” or “mild” for headache, myalgia, cough, and sore throat. A Phase II and a Phase III study conducted in North America (total of

over 600 influenza-positive patients) suggested up to 1 day of shortening of median time to this defined improvement in symptoms in patients receiving zanamivir compared with placebo, although statistical significance was not reached in either of these studies. In a study conducted in the Southern Hemisphere (321 influenza-positive patients), a 1.5-day difference in median time to symptom improvement was observed. Additional evidence of efficacy was provided by the European study.

Other Findings: There was no consistent difference in treatment effect in patients with influenza A compared with influenza B; however, these trials enrolled smaller numbers of patients with influenza B and thus provided less evidence in support of efficacy in influenza B.

In general, patients with lower temperature (e.g., 38.2°C or less) or investigator-rated as having less severe symptoms at entry derived less benefit from therapy.

No consistent treatment effect was demonstrated in patients with underlying chronic medical conditions, including respiratory or cardiovascular disease *[see Warnings and Precautions (5.4)]*.

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.

Pediatric Patients: The efficacy of RELENZA 10 mg inhaled twice daily for 5 days in the treatment of influenza in pediatric patients has been evaluated in a placebo-controlled study conducted in North America and Europe, enrolling 471 patients, ages 5 to 12 years (55% male, 90% Caucasian), within 36 hours of symptom onset. Of 346 patients with confirmed influenza, 65% had influenza A and 35% had influenza B. The definition of time to improvement included no fever and parental assessment of no or mild cough and absent/minimal muscle and joint aches or pains, sore throat, chills/feverishness, and headache. Median time to symptom improvement was 1 day shorter in patients receiving zanamivir compared with placebo. 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.

Although this study was designed to enroll children ages 5 to 12 years, the product is indicated only for children 7 years of age and older. This evaluation is based on the combination of lower estimates of treatment effect in 5- and 6-year-olds compared with the overall study population, and evidence of inadequate inhalation through the DISKHALER in a pharmacokinetic study *[see Use in Specific Populations (8.4), Clinical Pharmacology (12.3)]*.

14.2 Prophylaxis of Influenza

The efficacy of RELENZA in preventing naturally occurring influenza illness has been demonstrated in 2 post-exposure prophylaxis studies in households and 2 seasonal prophylaxis studies during community outbreaks of influenza. The primary efficacy endpoint in these studies was the incidence of symptomatic, laboratory-confirmed influenza, defined as the presence of 2 or more of the following symptoms: oral temperature ≥100°F/37.8°C or feverishness, cough,

headache, sore throat, and myalgia; and laboratory confirmation of influenza A or B by culture, PCR, or seroconversion (defined as a 4-fold increase in convalescent antibody titer from baseline).

Household Prophylaxis Studies: Two studies assessed post-exposure prophylaxis in household contacts of an index case. Within 1.5 days of onset of symptoms in an index case, each household (including all family members ≥5 years of age) was randomized to RELENZA 10 mg inhaled once daily or placebo inhaled once daily for 10 days. In the first study only, each index case was randomized to RELENZA 10 mg inhaled twice daily for 5 days or inhaled placebo twice daily for 5 days. In this study, the proportion of households with at least 1 new case of symptomatic laboratory-confirmed influenza was reduced from 19.0% (32 of 168 households) for the placebo group to 4.1% (7 of 169 households) for the group receiving RELENZA.

In the second study, index cases were not treated. The incidence of symptomatic laboratory-confirmed influenza was reduced from 19.0% (46 of 242 households) for the placebo group to 4.1% (10 of 245 households) for the group receiving RELENZA.

Seasonal Prophylaxis Studies: Two seasonal prophylaxis studies assessed RELENZA 10 mg inhaled once daily versus placebo inhaled once daily for 28 days during community outbreaks. The first study enrolled subjects 18 years of age or greater (mean age 29 years) from 2 university communities. The majority of subjects were unvaccinated (86%). In this study, the incidence of symptomatic laboratory-confirmed influenza was reduced from 6.1% (34 of 554) for the placebo group to 2.0% (11 of 553) for the group receiving RELENZA.

The second seasonal prophylaxis study enrolled subjects 12 to 94 years of age (mean age 60 years) with 56% of them older than 65 years of age. Sixty-seven percent of the subjects were vaccinated. In this study, the incidence of symptomatic laboratory-confirmed influenza was reduced from 1.4% (23 of 1,685) for the placebo group to 0.2% (4 of 1,678) for the group receiving RELENZA.

16 HOW SUPPLIED/STORAGE AND HANDLING

RELENZA is supplied in a circular double-foil pack (a ROTADISK) containing 4 blisters of the drug. Five ROTADISKs are packaged in a white polypropylene tube. The tube is packaged in a carton with 1 blue and gray DISKHALER inhalation device (NDC 0173-0681-01).

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) (see USP Controlled Room Temperature). Keep out of reach of children. Do not puncture any RELENZA ROTADISK blister until taking a dose using the DISKHALER.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (17.6).

17.1 Bronchospasm

Patients should be advised of the risk of bronchospasm, especially in the setting of underlying airways disease, and should stop RELENZA and contact their physician if they experience increased respiratory symptoms during treatment such as worsening wheezing,

shortness of breath, or other signs or symptoms of bronchospasm *[see Warnings and Precautions (5.1)]*. If a decision is made to prescribe RELENZA for a patient with asthma or chronic obstructive pulmonary disease, the patient should be made aware of the risks and should have a fast-acting bronchodilator available.

17.2 Concomitant Bronchodilator Use

Patients scheduled to take inhaled bronchodilators at the same time as RELENZA should be advised to use their bronchodilators before taking RELENZA.

17.3 Neuropsychiatric Events

Patients with influenza (the flu), particularly children and adolescents, may be at an increased risk of seizures, confusion, or abnormal behavior early in their illness. These events may occur after beginning RELENZA or may occur when flu is not treated. These events are uncommon but may result in accidental injury to the patient. Therefore, patients should be observed for signs of unusual behavior and a healthcare professional should be contacted immediately if the patient shows any signs of unusual behavior *[see Warnings and Precautions (5.3)]*.

17.4 Instructions for Use

Patients should be instructed in use of the delivery system. Instructions should include a demonstration whenever possible. For the proper use of RELENZA, the patient should read and follow carefully the accompanying Patient Instructions for Use.

If RELENZA is prescribed for children, it should be used only under adult supervision and instruction, and the supervising adult should first be instructed by a healthcare professional *[see Dosage and Administration (2.1)]*.

17.5 Risk of Influenza Transmission to Others

Patients should be advised that the use of RELENZA for treatment of influenza has not been shown to reduce the risk of transmission of influenza to others.

17.6 FDA-Approved Patient Labeling and Instructions for Use

See separate leaflet.

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