

**Relenza MedKit:
Potential Use for
Pandemic Influenza and
Proposed Development Plan**

**GlaxoSmithKline
Antiviral Drugs and Nonprescription Drugs
Advisory Committee Meeting
29 October 2008**

Relenza MedKit: GSK Objectives

- Respond to the HHS/BARDA request for the development of a Relenza Home Stockpiling product
- Provide a safe and effective anti-influenza therapy to be kept in the home for use during an influenza pandemic
 - As prescribed by the consumer's health care provider
 - To be used appropriately according to clear guidance and instructions
- Ensure involvement of critical Public Health Authorities:
 - Local Departments of Health: to provide clear instructions for appropriate timing of use (Pandemic Alert Phase)
 - National Public Health Authorities: to provide national endorsement of antiviral home stockpiling and guidance and instruction to Local Public Health Departments for individual local communication plans that are consistent with an overall national strategy

Relenza MedKit: Potential Risks

- **Safety**
 - Use in patients for whom Relenza is not recommended
 - Change in medical conditions over time, with no reassessment of risk/benefit to individual patient
 - Potential for unsafe storage of the MedKit leading to access by unintended users (young children)
 - Inappropriate use for non-pandemic influenza situations
- **Efficacy**
 - Unknown medical benefit against pandemic strains of influenza
 - Inappropriate retention or use of MedKit past product expiry
 - Inappropriate storage of MedKit under extreme conditions
- **Resistance**
 - Suboptimal use causing antiviral resistance

Relenza MedKit: Potential Benefits

- **Improved Access to Relenza during pandemic influenza**
 - Greater and more immediate access to antiviral medications for a larger proportion of the general public
 - Access during resource limited situation
 - Limited healthcare services may be severely limited
 - Severely limited manufacturing capacity and drug availability
 - Potential for central distribution failure of government stockpiles
- **Containment of Pandemic Influenza**
 - Maintains social distancing while allowing access to antiviral medication
 - Augments the capacity of antivirals to contribute to the containment of pandemic spread
- **Increased numbers of patients protected or treated**
 - Improved survival – decreased morbidity and mortality
 - Provides a bridge to vaccination during lag time prior to vaccine availability and onset of vaccine efficacy

Relenza MedKit: Development Objectives

- **Respond adequately to request from BARDA**
 - Provision of antivirals to appropriate lay individuals in advance of an influenza pandemic to enhance overall preparedness
 - Mechanism for “Home Stockpiling” of antivirals for the treatment or household prophylaxis of influenza
- **Protect Patient Safety through proper use instructions to ensure**
 - Use by appropriate patient population
 - Correct use of the inhaler device
 - Correct use within the appropriate situations
- **Minimize Antiviral Resistance Risk through proper warnings and instructions around inappropriate use**

Relenza Inhalation Powder: Indications

- **Potent and highly selective inhibitor of the influenza virus neuraminidase (NA)**
- **Efficacy and safety in the treatment and prophylaxis of influenza A and B infections demonstrated through an extensive program of clinical studies**
 - **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)**

Relenza: Potential in Pandemic Influenza - Stockpiling

- **Molecular target (NA) highly conserved across Influenza A strains**
 - Antiviral activity should be conserved
 - In vitro activity against potential pandemic strains:
 - H5N1, H2N2 and H9N2
 - In vivo animal model efficacy against H5N1
- **Clinical efficacy in seasonal influenza plus in vitro/in vivo activity against potential pandemic strains gives confidence that Relenza will be useful in pandemic influenza**
- **United States' Pandemic Preparedness Plan:**
 - Stockpile enough antivirals to cover 25% of the US population or approximately 81 million antiviral courses
 - Other governments and private corporations have initiated similar stockpiling programs

Relenza MedKit: Home Stockpiling Concerns

- **Acceptance of stockpiling by governments and large corporations**
- **Potential utility of home stockpiling to widen protected population during a pandemic**
- **Concern that current data does not reflect a supportive risk:benefit profile**
 - **IDSA, ACP, AMA, AAP, AAFP, and SHEA have expressed concerns around inappropriate use of and drug resistance**

Relenza: Safety in Clinical Development Program

- Phase II and Phase III clinical trials enrolled over 14,000 subjects
 - 7,000 subjects received zanamivir by the inhaled route
- AE frequency from six Phase II and Phase III treatment studies:
 - 38% for placebo subjects
 - 33% for zanamivir subjects
- AE frequency from six Phase III prophylaxis studies:
 - 51% - 58% for placebo, rimantidine, and zanamivir subjects
- Most commonly reported AEs consistent with signs and symptoms of influenza
- 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

Relenza: Post-Marketing Safety

- **1408 spontaneous adverse event reports received by GSK**
- **Estimated postmarketing exposure (worldwide) = 7.6 million treatment courses**
 - **From March 1999, date of zanamivir first launch, through to 31 July 2008**
- **The majority of cases originated in Japan (52.5%), USA (16.6%), Canada (9.2%) and Germany (6.5%)**
 - **21.0% Psychiatric disorders**
 - **Majority (67%) from Japan in 2007**
 - **16.8% Respiratory, Thoracic, Mediastinal Disorders**

Relenza: Neuropsychiatric Disorders

- **Spike in spontaneous neuropsychiatric AE reports in children and adolescents from Japan in Spring 2007 prompted close review of data**
 - 145 cases reported to GSK during 2006 – 07 season
- **No convincing evidence of a causal association for accidents, neurological or psychiatric events, including convulsions, loss of consciousness, suicidal ideation, depression, or self-harm behavior**
 - Reviewed with Pediatric Advisory Committee in November 2007
- **USPI updated to include information in Warnings and Precautions, Adverse Reactions, and Patient Counseling**

Relenza: Bronchospasm

- **Spontaneous reporting of respiratory AEs, particularly bronchospasm, in 2000 prompted USPI label change in Warning and Precautions**
 - Not recommended for treatment or prophylaxis of influenza in individuals with underlying airways disease (such as asthma or chronic obstructive pulmonary disease)
- **Period analyses of reported respiratory AEs to GSK**
 - Most recent analysis encompassed 1 August 2005 to 31 July 2008
 - Few cases have been identified since 2001
 - No additional changes to the label warranted

Relenza: Resistance

- **In vitro: Difficult to select zanamivir resistance mutations**
 - Requires several passages under high zanamivir concentrations
 - Compared with one or two passes for amantadine
 - Has been reported in influenza A (human and avian)
 - E119G, R292K, double mutant
- **Clinical Isolates:**
 - To date, 1 zanamivir resistant isolate recovered from immunocompromised child treated for 15 days with nebulized formulation
 - Influenza B: R152K

Relenza: Cross Resistance

- **Clinical Isolates resistant to oseltamivir have been identified**
 - Resistant strains containing these mutations retain sensitivity to zanamivir
 - H274Y, E119V, N294S and I221T
- **Influenza A/H1N1 with mutation H274Y**
 - Observed worldwide since 2007
 - Increasing prevalence within circulating isolate samples
 - Northern Hemisphere 2007-2008 = 16%
 - Southern Hemisphere 2008 = 39%
 - H274Y confers a 900 fold decrease in sensitivity to oseltamivir
 - Remains fully sensitive to zanamivir
 - H274Y has been observed in H5N1 isolates
- **Support HHS recommendations to include both oseltamivir and zanamivir within stockpiling programs**

Relenza: Compound Characteristics Affecting Resistance Potential

- **Target highly conserved, essential region of NA**
 - Close mimic of natural substrate
- **Topical application allows high local drug concentrations at the site of viral replication**
- **Relenza treatment shown to result in rapid reductions in respiratory viral titers compared to untreated**
 - Rapid decrease in viral replication
- **All impact negatively on mechanisms of antiviral resistance generation**

Relenza MedKit: Development Program

- **Seeks to address the identified risks**
 - **Appropriate use**
 - **Safety and Antiviral resistance**
- **Comprised of four studies designed around critical questions regarding these risks**
 - **Development program carefully designed to incorporate best practices for studies supporting a product to be used at home by a consumer**

Relenza MedKit: Key Proposed Contents

- Quick Guide Consumer Brochure: Instructions for use of the MedKit
 - Includes self diagnosing algorithm
 - Currently under development by CDC
- Practice Diskhaler: Diskhaler requiring assembly without active drug
 - To be used in conjunction with the Instructions for Use
- Instructions for Use: Instructions on how to assemble and use the Diskhaler device
- Relenza (zanamivir) Inhalation Powder: Drug product
 - Packaged separately (similar to current commercial packaging)
 - Provided within the MedKit

Relenza MedKit: Development Program

Label Comprehension Study

Can consumers understand the product's use, directions, and warnings in the labeling? (Test Quick Guide Consumer Brochure)



Human Factors Study

Can consumers assemble and use the device correctly?
(Test Instructions for Use + Practice Diskhaler Assembly & Use)



Compliance Study: During 1 Influenza Season

Can consumers retain the product and not use it during an active influenza season?
(Use only for announced pandemic flu in local area; Compliance with storing and locating; Randomized to 1 of 2 pandemic scenarios)



Extended Compliance Study: During 2 Influenza Seasons

Can consumers retain the product and not use it during an active influenza season?
(Use only for announced pandemic flu in local area;
Compliance with storing and locating)

Relenza MedKit: Label Comprehension Study

- Rationale and Objectives: to test the effectiveness of the Quick Guide Consumer Brochure around key communication objectives
 - Intended use (purpose, when to use)
 - Directions for use (prevention/treatment)
 - Warnings
- Study Populations
 - Cohort 1: Normal health literacy, ages 16+ (n = 175)
 - Cohort 2: Low health literacy, ages 16+ (n=175)

Relenza MedKit: Label Comprehension Study

- *1 Day test*
- *Interview*
- *No drug dispensed*
- *Labeling reviewed as it will be in market*
- *3rd party scenarios used to test comprehension*
- *Learnings used to refine labeling*

Recruit: General population



CDA



Health Literacy Testing



Review Labeling



Scenario questions
(3rd party)



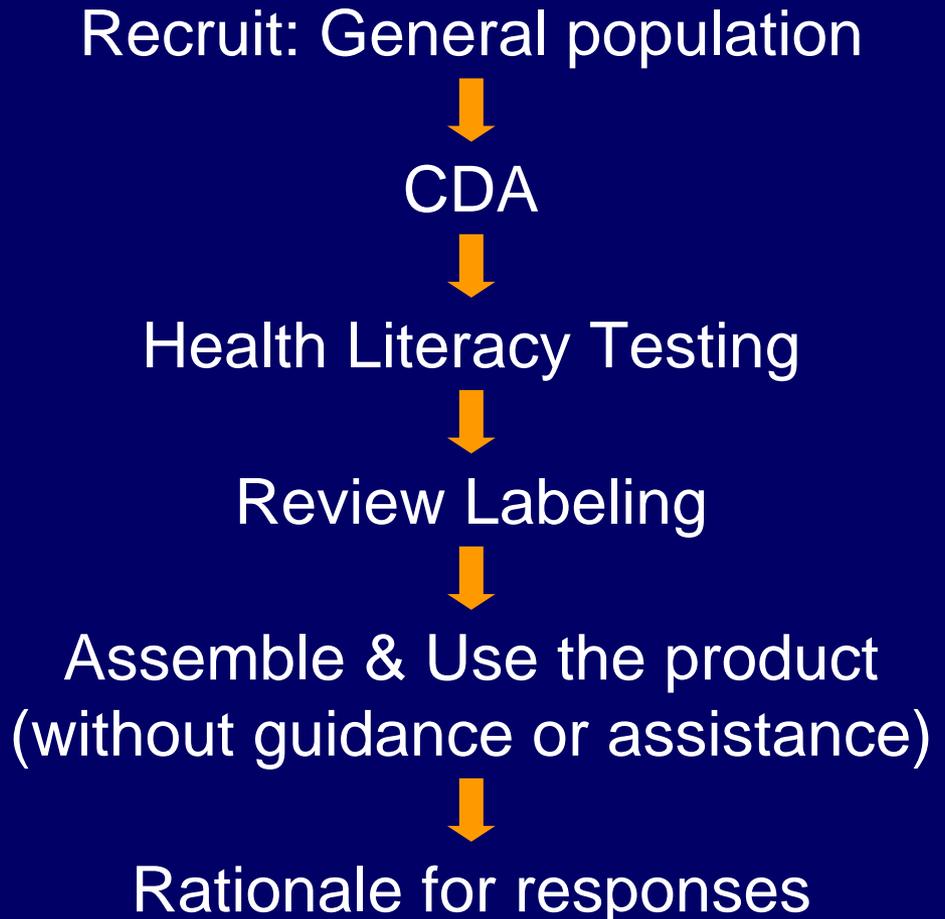
Rationale for responses

Relenza MedKit: Human Factors Study

- **Rationale and Objectives:** to test the consumer's comprehension of the device instructions and ability to manipulate and use the Diskhaler device correctly
 - Assemble and use the device correctly
 - Based on the Diskhaler Instructions for Use
 - Including nine specific directions that will be evaluated
- **Study Populations**
 - Cohort 1: Normal health literacy, ages 16+ (n=175)
 - Cohort 2: Low health literacy, ages 16+ (n=175)
 - Cohort 3: Parents of children ages 5-15 and child's ability to inhale with the device (n=175)

Relenza MedKit: Human Factors Study

- *1 Day test*
- *Observation*
- *No drug dispensed*
- *Labeling reviewed as it will be in market*
- *Subject assembles & uses the Diskhaler (no drug)*
- *Learnings used to refine labeling*

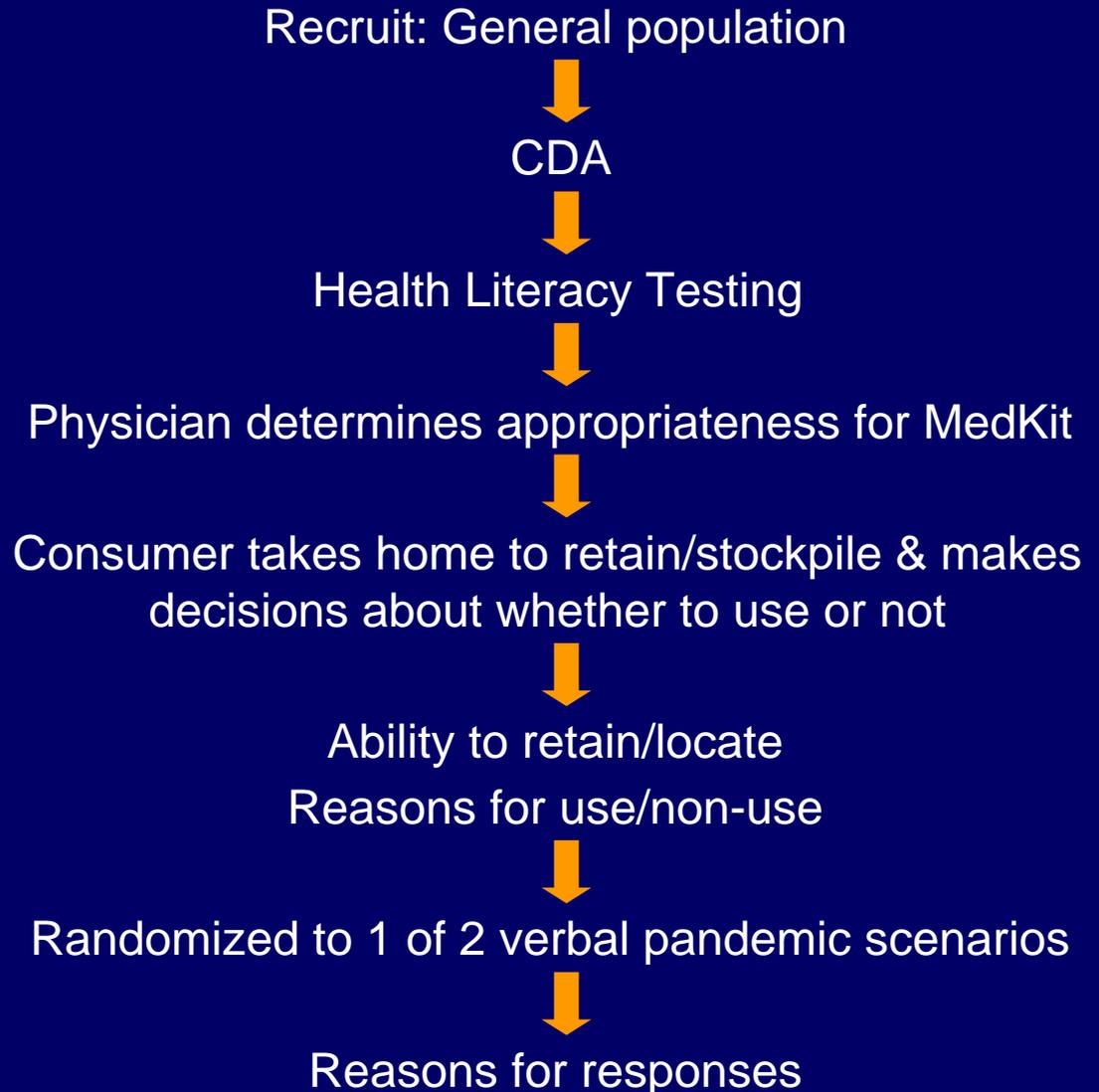


Relenza MedKit: Compliance Study

- Rationale and Objectives: Targeted compliance study conducted in two parts:
 - (1) 3 month, at-home product retention portion to evaluate a consumer's ability to retain the MedKit and avoid use during an active influenza season
 - (2) pandemic scenario portion to evaluate a subject's ability to make the appropriate decisions within a verbal pandemic scenario
 - Through verbalization of the actions that they would take in the given scenario based on their judgment and the product labeling
 - Incorporates aspects of the pandemic flu stockpiling plan being created by HHS, CDC and FDA
- Study Populations
 - Cohort 1: Adults, ages 16+ (n=150)
 - Cohort 2: Parents of children ages 5-15 (n=150)

Relenza MedKit: Compliance Study

- **3 month at-home retention**
- **1 active influenza season (early information on use behavior)**
- **Uncontrolled, open-label**
- **Active drug dispensed**
- **Packaging & Labeling as it will be in market**
- **Subject makes decisions about use based on labeling & judgment**



Relenza MedKit: Extended Compliance Study

- Rationale and Objectives: this study will not be conducted if the single compliance study approach suggested by FDA can be utilized
- This study is similar to the Compliance Study already discussed with two exceptions:
 - The in-home retention period will be 15 months for this study vs. 3 months for the compliance study
 - 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

Relenza MedKit: Development Program Summary

- **Designed to address identified safety and resistance risk**
 - **Better define risk:benefit of home stockpiling Relenza in a MedKit for pandemic influenza**
- **Designed to generate the appropriate data to support a product to be used at home by a consumer without recent input from or assessment by the prescriber**

Relenza MedKit: Conclusions

- **GSK committed to working with the critical Public Health authorities and the FDA**
 - Relenza MedKit Product with optimized labeling and instructions
 - Maximize benefit and minimize risk
- **Proposed MedKit development plan**
 - Consistent with these goals
 - Consistent with National Pandemic Preparedness Plans
- **Safety and Efficacy of Relenza MedKit for Home Stockpiling requires:**
 - Clear guidelines around appropriate prescription for health care providers
 - Clear instructions for the patient/consumer on how and when the Relenza MedKit should be used during an influenza pandemic
 - Critical Public Health authorities must be fully engaged