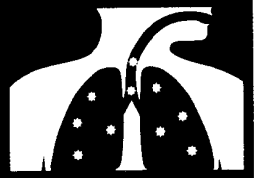
Get RELENZA–A timely advance in flu treatment

Often mistaken for a common cold or stomach flu, influenza—or the flu—is actually a viral infection in your lungs. Having the flu usually means a miserable time just waiting it out—and missing out. This year, your doctor can prescribe RELENZA, the first inhaled flu treatment that helps put you back in charge. So when the flu virus gets you, you can get it back, and get back to your life—sooner.



Flu–It's in the lungs

Even though you feel it all over, the flu virus lives mostly in your lungs. It's called a respiratory infection because the virus actually invades your lungs, where it starts to multiply. RELENZA is an antiviral medicine you breathe in to help shorten the time you have the flu.

RELENZA is available by prescription only. If side effects occur, they are generally mild and similar to placebo. The most common are sinusitis, nausea, and diarrhea—which occur in 3% or less of patients.

RELENZA–Inhaled medicine that helps you get over the flu

Fight flu with the first inhaled treatment

Unlike over-the-counter medicines that treat flu symptoms, inhaled prescription RELENZA works on the virus itself. RELENZA has been found to work against the most common types of influenza virus in patients 12 and older. Because RELENZA works differently, it may take several days to feel relief.

RELENZA should be taken within 2 days of the first signs of the flu, and can actually help shorten the duration of the flu. Just two inhalations twice a day for 5 days can help you get over the flu faster and back to what's important. But only your health-care provider can diagnose the flu, so call early for the best results.

This year when you get the flu, get RELENZA, and get over it...sooner!

Patients with chronic lung disease should consult their healthcare professional, and those with severe lung disease may be at risk of wheezing. You should be shown how to use the DISKHALER®.

Please see important product information inside this brochure.

RELENZA®

ZANAMIVIR FOR INHALATION

Is it the flu? Here's a checklist...

One moment you're fine, the next you're miserable. When symptoms come on that fast and strong, chances are it's not a cold—it may be the flu. But only your healthcare professional can be sure. Complete the checklist below—the more checks you make, the more likely it's the flu.

Common symptoms of the flu

- ☐ Fatigue
- ☐ Fever (100°F–104°F)
- ☐ Body aches
- ☐ Loss of appetite
- ☐ Headache
- ☐ Severe cough
- ☐ Have you recently been around someone who has the flu?

If you have these symptoms, call your healthcare professional immediately.

RELENZA®

ZANAMIVIR FOR INHALATION

The flu— don't take it lying down

Catch the fever early this flu season

RELENZA can help reduce the time you suffer from the misery of the flu. Take charge early this flu season by monitoring your symptoms. Since fever is one of the early warnings of the flu, keep this thermometer close at hand.

If you have symptoms of the flu, call your healthcare professional immediately.

RELENZA®

ZANAMIVIR FOR INHALATION

Helps get you over the flu—sooner.

For more information, talk to your healthcare professional or visit our web site at: www.relenza.com

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GlaxoWellcome
Glaxo Wellcome Inc.
Research Triangle Park, NC 27709
Web site: www.glaxowellcome.com

RELENZA®

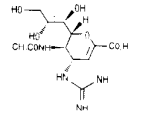
PRODUCT INFORMATION

(zanamivir for inhalation)

For Oral Inhalation Only

For Use with the DISKHALER® Inhalation Device

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 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. 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. In a study of 5 adult and 5 adolescent patients with obstructive airway diseases, the combined peak inspiratory flow rates ranged from 66 to 140 L/min.

MICROBIOLOGY:

Mechanism of Action: The proposed mechanism of action of zanamivir is via inhibition of influenza virus neuraminidase with the possibility of alteration of virus particle aggregation and release.

Antiviral Activity In Vitro: 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% inhibitory concentrations (IC_{50} and IC_{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 µg/mL). The relationship between the in vitro inhibition of influenza virus by zanamivir and the inhibition of influenza virus replication in humans has not been established.

Drug Resistance: Influenza viruses with reduced susceptibility to zanamivir have been recovered in vitro by passage of the virus in the presence of increasing concentrations of the drug. Genetic analysis of these viruses showed that the reduced susceptibility in vitro to zanamivir is associated with mutations that result in amino acid changes in the viral neuraminidase or viral hemagglutinin or both.

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 mutation (Thr 198 Ile) which resulted in a reduced affinity for human cell receptors, and a mutation in the neuraminidase active site (Arg 152 Lys) which reduced the enzyme's activity to zanamivir by 1000-fold.

Insufficient information is available to characterize the risk of emergence of zanamivir resistance in 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 clear 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 influenza A, and to a more limited extent for influenza B, 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.

CLINICAL PHARMACOLOGY:

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 ($AUC_{0-\infty}$) ranged from 111 to 1364 ng•h/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/h. Unabsorbed drug is excreted in the feces.

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

Impaired Renal Function: Systemic exposure is limited after inhalation (see Absorption and Bioavailability). 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/h, mild/moderate 2.7 L/h, and severe 0.8 L h; median values) and significant increases in half-life (normals 3.1 h, mild/moderate 4.7 h, and severe 16.5 h; median values) and systemic exposure were observed. Safety and efficacy have not been documented in the presence of severe renal insufficiency.

Pediatric Patients: The pharmacokinetics of zanamivir have not been studied in pediatric patients under 12 years of age with influenza (see PRECAUTIONS: Pediatric Use).

Geriatric Patients: The pharmacokinetics of zanamivir have not been studied in patients over 65 years of age (see PRECAUTIONS: Geriatric Use).

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, $AUC_{0-\tau}$, C_{max}, $T_{1/2}$, 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.

Drug Interactions: No clinically significant pharmacokinetic drug interactions are predicted based on data from in vitro studies.

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.

INDICATIONS AND USAGE: RELENZA is indicated for treatment of uncomplicated acute illness due to influenza virus in adults and adolescents 12 years and older who have been symptomatic for no more than 2 days. This indication is based on studies in which the predominant influenza infections were influenza A, and a limited number of patients with influenza B were also enrolled (see Description of Clinical Studies and PRECAUTIONS).

effect varied between studies, with possible relationships to population related factors including amount of symptomatic relief medication used.

Populations Studied: The principal phase 3 studies enrolled 1588 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 1164 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 2 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 2 and a phase 3 study conducted in North America (total of over 600 influenza-positive patients) suggested up to one day of shortening of median time to this defined improvement in symptoms in patients receiving zanamivir compared to 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 to 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 (see PRECAUTIONS).
- 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 PRECAUTIONS).
- 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.

CONTRAINDICATIONS: RELENZA is contraindicated in patients with a known hypersensitivity to any component of the formulation.

PRECAUTIONS:

General: Patients should be instructed in the use of the delivery system. Instructions should include a demonstration whenever possible. Patients should read and follow carefully the Patient Instructions for Use accompanying the product. Effective and safe use of RELENZA requires proper use of the DISKHALER to inhale the drug.

There is no evidence for efficacy of zanamivir in any illness caused by agents other than influenza virus A and B. Data on treatment of influenza B are limited (see INDICATIONS AND USAGE: Description of Clinical Studies).

No data are available to support safety or efficacy in patients who begin treatment after 48 hours of symptoms.

Safety and efficacy of repeated treatment courses have not been studied.

Patients with Underlying Respiratory Disease: Safety and efficacy have not been demonstrated in patients with underlying chronic pulmonary disease. In particular, this product has not been shown to be effective, and may carry risk, in patients with severe or decompensated chronic obstructive pulmonary disease or asthma. 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 1 study. In interim results from an ongoing treatment study in patients with acute influenza-like illness superimposed on underlying asthma or chronic obstructive pulmonary disease, more patients on zanamivir than on placebo experienced greater than 20% decline in FEV$_1$ or peak expiratory flow rate. Some patients with underlying respiratory disease may experience bronchospasm and/or decline in lung function when treated with zanamivir. Any patient who develops bronchospasm or decline in lung function should stop the drug. Patients with underlying respiratory disease should be instructed to have a fast-acting inhaled bronchodilator available when treated with zanamivir.

Prevention of Influenza: Use of zanamivir should not affect the evaluation of individuals for annual influenza vaccination in accordance with guidelines of the Centers for Disease Control and Prevention Advisory Committee on Immunization Practices. Safety and efficacy of zanamivir have not been established for prophylactic use of zanamivir to prevent influenza.

Limitations of Populations Studied: Safety and efficacy have not been demonstrated in patients with high-risk underlying medical conditions (see INDICATIONS AND USAGE: Description of Clinical Studies). 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.

Information for Patients: 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.

Patients should be advised to finish the entire 5-day course of treatment even if they start to feel better sooner.

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.

Patients with asthma or chronic obstructive pulmonary disease should be advised of the potential risk of bronchospasm with zanamivir, should have a fast-acting inhaled bronchodilator available, and should stop zanamivir and contact their physician promptly if they experience worsening respiratory symptoms. Patients scheduled to take inhaled bronchodilators at the same time as RELENZA should be advised to use their bronchodilators before taking RELENZA.

Drug Interactions: No clinically significant pharmacokinetic drug interactions are predicted based on data from in vitro studies.

Carcinogenesis, Mutagenesis, and 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 per 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-per-day IV dose, AUC values ranged between 142 and 199 mcg•h/mL (>300 times the human exposure at the proposed clinical dose).

Pregnancy: Pregnancy Category B. 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. Pre- and post-natal developmental studies were performed in rats (dosed from day 16 of pregnancy until litter day 21 to 23). In all studies, intravenous (1, 9, and 90 mg/kg per day) instead of the inhalational route of drug administration was used. No malformations, maternal toxicity, or embryotoxicity were observed in pregnant rats or rabbits and their fetuses. Because of insufficient blood sampling timepoints in both

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.

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.

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.

Pediatric Use: Safety and effectiveness in pediatric patients below 12 years of age have not been established. In the three principal phase 3 treatment 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.

Geriatric Use: Of the total number of patients in 6 clinical treatment studies of RELENZA, 59 were 65 and over, while 24 were 75 and over. No overall differences in safety or effectiveness were observed between these subjects 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.

ADVERSE REACTIONS: 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 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

	RELENZA		
Adverse Event	10 mg b.i.d. Inhaled (n=1132)	All Dosing Regimens* (n=2289)	Placebo (Lactose Vehicle†) (n=1520)
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, & 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.

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

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 3 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.

See PRECAUTIONS for safety information in patients with underlying respiratory disease.

OVERDOSAGE: There have been no reports of overdosage from administration of RELENZA. Doses of zanamivir up to 64 mg/day have been administered by nebulizer. Additionally, doses of up to 1200 mg/day for 5 days have been administered intravenously. Adverse effects were similar to those seen in clinical studies at the recommended dose.

DOSAGE AND ADMINISTRATION: RELENZA is for administration to the respiratory tract by oral inhalation only, using the DISKHALER device provided. **Patients should be instructed in the use of the delivery system. Instructions should include a demonstration whenever possible.**

The recommended dose of RELENZA for treatment of influenza in patients ≥12 years of age is 2 inhalations (one 5-mg blister per inhalation for a total dose of 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. There are no data on the effectiveness of treatment with RELENZA when initiated more than 2 days after the onset of signs or symptoms.

Patients scheduled to use an inhaled bronchodilator at the same time as RELENZA should use their bronchodilator before taking RELENZA. (See PRECAUTIONS regarding patients with chronic respiratory disease and other medical conditions.)

HOW SUPPLIED: 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.

GlaxoWellcome

Glaxo Wellcome Inc.
Research Triangle Park, NC 27709

US Patent Nos. 4,627,432; 4,778,054; 4,811,731; 5,360,817; 5,648,379; 5,035,237; Des. 379,506.

July 1999 RL-726

Zanamivir in the management of influenza A & B

RELENZA®

ZANAMIVIR FOR INHALATION

Physician Slide Kit

GlaxoWellcome

Table of contents

Slide 1

Zanamivir in the management of influenza A & B

RELENZA®
(zanamivir for inhalation)

The first inhaled antiviral for influenza A & B

GlaxoWellcome

Zanamivir in the management of influenza A & B

This presentation focuses on RELENZA and its impact on the management of influenza A and B.

RELENZA is the first of a new class, neuraminidase inhibitors, for treatment of influenza A and B.

References: 1. Sullivan KM. Health impact of influenza in the United States. *PharmacoEconomics.* 1996;9(suppl 3):26-33. **2.** Nichol KL, Margolis MD, Wuorenma J, Von Sternberg T. The efficacy and cost effectiveness of vaccination against influenza among elderly persons living in the community. *N Engl J Med.* 1994;33:778-784. **3.** Centers for Disease Control and Prevention. *Influenza Fastats.* Available at: http://www.cdc.gov/nchswww/fastats/flu.htm. Accessed August 30, 1999.

Slide 2

Influenza:
A significant public health issue

- Approximately 314,000 hospitalizations annually due to influenza and its complications[1]
- 20,000 to 40,000 influenza-related deaths each year[1]
- Annual direct and indirect costs totaling over $12 billion[2]
- 75 million lost workdays per year[3]

1. Sullivan KM. *PharmacoEconomics.* 1996
2. Nichol KL. *N Engl J Med.* 1994
3. Centers for Disease Control and Prevention. Available at: http://www.cdc.gov/nchswww/fastats/flu.htm Accessed 1999

The burden of influenza: significant morbidity and mortality

Influenza is a serious disease affecting 108 million Americans in a given year—with 20,000 to 40,000 influenza-related deaths.[1,2]

The burden of influenza: the economic impact

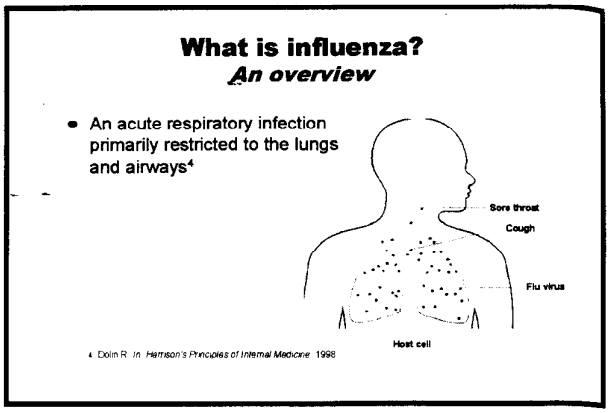
The reality of influenza is that it's more than just a nuisance in the workplace and the medical community. Influenza illness results in:

–Approximately 303 million days of restricted activity.[3]

–Up to 24 million medical care visits annually.[1]

RELENZA®
ZANAMIVIR FOR INHALATION

Slide 3



Influenza: an overview

Although often perceived as a systemic infection, influenza is actually an acute respiratory infection with virus rarely detected in extrapulmonary sites, including the bloodstream.[4]

Some brief facts[4]:

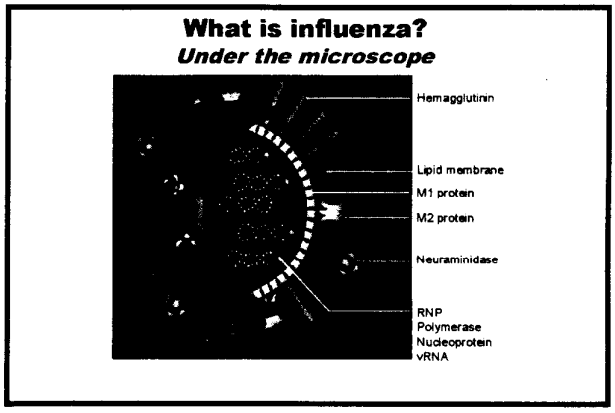
–Onset is typically abrupt and characterized by fever and upper respiratory manifestations such as sore throat and cough.

–Cytokine release induces systemic symptoms such as headache, myalgia, and malaise.

–Spread via airborne droplets, usually by coughing and sneezing.

–Although infection can occur throughout the year, epidemics usually occur during winter months.

Slide 4



The influenza virus: under the microscope[5]

The influenza virus is a negative-strand RNA virus with a segmented genome. It is an enveloped virus, 80 to 120 nm in diameter and covered with surface glycoprotein antigen spikes.

Influenza A and B viruses have eight RNA segments. These segments are independently encapsulated by the viral nucleoprotein (NP), and each segment is associated with a polymerase complex.

Hemagglutinin helps the virus attach to healthy cells. Neuraminidase helps release the virus from infected cells and may help it to breach cell membranes.

References: 4. Dolin R. Influenza. In: Fauci AS, Braunwald E, Isselbacher KJ, et al, eds. *Harrison's Principles of Internal Medicine.* 14th ed. New York, NY: McGraw-Hill; 1998:1112-1116. **5.** Ruigrok RWH. Structure of Influenza A, B and C Viruses. In: Nicholson KG, Webster RG, Hay AJ. *Textbook of Influenza.* London, England: Blackwell Science; 1998:29-42.

RELENZA®

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Slide 5

The essential role of neuraminidase

Membrane spike protein containing the receptor-destroying activity necessary for release of newly formed virus from the surface of an infected cell[6]

6. Colman PM. In: *Textbook of Influenza*. 1998.

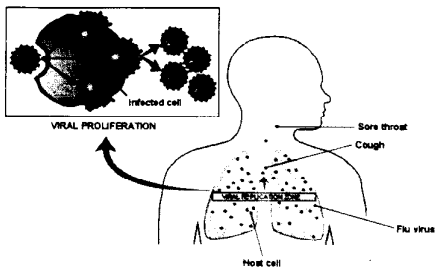
The essential role of neuraminidase[6]

A critical component of the influenza virus is the spike protein neuraminidase (NA). This enzyme is crucial for the destruction of the influenza virus receptor, permitting the release of newly formed virus from the surface of the infected cell. When neuraminidase is inhibited, the viral replication cycle can be stopped.

Based on the understanding that continued viral replication leads to the development of influenza symptoms, it is evident that breaking the cycle of influenza infection by use of a specific neuraminidase inhibitor has the potential to deliver real clinical benefit.

Slide 6

The viral replication zone



The viral replication zone[5]

Virus is deposited in respiratory epithelium, where hemagglutinin helps it to attach to and penetrate columnar epithelial cells. The virion then begins a 4- to 6-hour replication cycle until cell death.

Neuraminidase enzymes facilitate replication by aiding the release of mature virions from infected cells. New copies of the virus are released to continue replication in nearby cells.

References: 5. Ruigrok RWH. Structure of Influenza A, B, and C Viruses. In: Nicholson KG, Webster RG, Hay AJ. *Textbook of Influenza.* London, England: Blackwell Science; 1998:29-42. **6.** Colman PM. Structure and Function of the Neuraminidase. In: Nicholson KG, Webster RG, Hay AJ. *Textbook of Influenza.* London, England: Blackwell Science; 1998:65-73.

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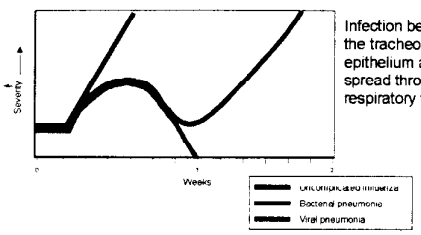
Slide 7

The course of influenza in untreated patients

Progression of influenza infection[7]



Infection begins in the tracheobronchial epithelium and can spread throughout the respiratory tract

Adapted from Small PA Jr. *Hospital Practice*. 1990

The course of influenza in untreated patients[7]

If influenza is presented early enough, the progression of influenza can be shortened; however, after 1 to 2 days of incubation, the course of influenza may take one of three paths:

1. Uncomplicated influenza
   - –Peaks on about days 3 to 5, then abates;
   - –Recovery is usually complete in about 1 week.
2. Influenza and bacterial pneumonia
   - –Recovery halts, and symptoms progressively worsen.
3. Viral pneumonia
   - –Rapid onset, with symptoms apparent as early as day 1 of infection.

Slide 8

Host defense against influenza

- Neutralizing antibodies directed against the viral membrane glycoprotein, HA
- CD8+ T cells
- Complement, NK cells, and macrophages
- CTL
- CD4+ T cells
- Cytokines

Host defense against influenza[8,9]

The primary defense mechanism against influenza infection is the neutralizing antibodies directed against hemagglutinin. CD8+ T cells clear influenza infection from the lung. The activity of complement, natural killer (NK) cells, and macrophages alone is insufficient. Cytotoxic T-lymphocytes (CTL) eliminate virus-infected cells, while antibody neutralizes free virions before more cells are infected. CD4+ T cells do not play a major effect or role, but they do play a major part in coordinating the immune response. They are essential for antibody and cytokine production.

References: 7. Small PA Jr. Influenza: pathogenesis and host defense. *Hospital Practice.* November 15, 1990:51-62. **8.** Thomas DB. Antibody-Mediated Immunity. In: Nicholson KG, Webster RG, Hay AJ. *Textbook of Influenza.* London, England: Blackwell Science; 1998:267-277. **9.** Stevenson PG and Doherty PC. Cell-Mediated Immune Response to Influenza Virus. In: Nicholson KG, Webster RG, Hay AJ. *Textbook of Influenza.* London, England: Blackwell Science; 1998:278-287.

Slide 9

Cytokine involvement

- Cytokine release is associated with systemic symptom formation and host defense[10]
- IL-6 and IFN-α are the primary cytokines associated with influenza symptoms[10]
- IL-6 appears to be the main cause of fever[10]
- IFN-α induces NK cell activity[10]

10. Hayden FG, et al. *J Clin Invest.* 1998.

Cytokine involvement[10]

Cytokine release is associated with systemic symptom formation and host defense. Recent studies have indicated that interleukin-6 (IL-6) and interferon-alpha (IFN-α) play a major role in symptom formation. For example, the high fever observed with influenza infection is associated with the release of IL-6. IFN-α appears to be responsible for early systemic and local symptoms of influenza infection. IFN-α is also responsible for the induction of NK cell activity. Additional cytokines of importance are tumor necrosis factor-alpha (TNF-α) and IL-8. Peak levels of these cytokines are observed relatively late in influenza infection. These proinflammatory cytokines are possibly more involved in severe influenza infection that is centered in the lower respiratory tract.

Slide 10

Cytokine response

- Influenza infection is localized within the respiratory tract, but the release of cytokines produces a systemic response[10]
- Systemic symptoms induced by this cytokine response include myalgia, malaise, and fever[10]

10. Hayden FG, et al. *J Clin Invest.* 1998.

Cytokine response[10]

Cytokines associated with influenza infection are produced and consumed within the respiratory mucosa. However, cytokines do enter the circulation to induce a systemic response to the infection. Systemic symptoms induced by the release of cytokines include myalgia, malaise, and fever. Studies have shown that systemic symptom onset is associated with increased levels of IL-6. In addition, when IL-6 is administered to human subjects, it causes an acute, febrile illness with systemic symptoms similar to those observed with influenza infection. A flu-like illness including fever, myalgia, and malaise develops when IFN-α is administered in a therapeutic capacity to individuals with chronic viral hepatitis. These data suggest that while influenza infection is localized within the respiratory tract, the production of cytokines induces a systemic response that produces the symptoms associated with influenza infection.

Reference: 10. Hayden FG, Fritz RS, Lobo MC, et al. Local and systemic cytokine responses during experimental human influenza A virus infection. *J Clin Invest.* 1998; 101(3):643-649.

Slide 11

Is it a cold or is it the flu?

Symptoms	INFLUENZA	COMMON COLD
Onset	Abrupt	More gradual
Cough	Common, severe	Mild to moderate
Malaise	Severe	Mild
Fever	Common—100°-104°F	Uncommon or only 1°F increase
Myalgia	Severe, common	Uncommon
Arthralgia	Severe, common	Uncommon
Anorexia	Common	Uncommon
Headache	Severe, common	Mild, uncommon
Prostration	Early & prominent	Rarely
Chest discomfort	Common, severe	Mild to moderate
Stuffy nose	Occasional	Common
Sneezing	Occasional	Common

Is it a cold or is it the flu?

Early flu symptoms can be mistaken for a common cold, but there are significant differences[4,11]:

–Weakness, fever, headache, and muscle aches are specific hallmarks of influenza infection that are rarely present with a cold.

–Patients often refer to gastrointestinal illness as the "stomach flu"; however, influenza rarely causes gastrointestinal symptoms.

References: 4. Dolin R. Influenza. In: Fauci AS, Braunwald E, Isselbacher KJ, et al, eds. *Harrison's Principles of Internal Medicine.* 14th ed. New York, NY: McGraw-Hill; 1998:1112-1116. **11.** Public Health Service, US Department of Health and Human Services. Fact Sheet: Flu. Available at: http://www.niaid.nih.gov/factsheets/flu.htm. Accessed September 1, 1999.

Slide 12

RELENZA®
(zanamivir for inhalation)

The first inhaled antiviral that fights both influenza A & B at the primary site of viral replication

- The first neuraminidase inhibitor
- Delivers antiviral action to the respiratory tract—the primary site of viral replication
- Helps stop viral replication and shortens the misery of flu A & B
- Very favorable safety profile

Indicated for the treatment of uncomplicated acute illness due to influenza virus in adults and adolescents 12 years and older who have been symptomatic for no more than 2 days.

RELENZA–The first inhaled antiviral that fights both influenza A & B at the primary site of viral replication

RELENZA offers a logical approach to combatting influenza infection:

–The proposed mechanism of action of zanamivir is via inhibition of influenza virus neuraminidase with the possibility of alteration of virus particle aggregation and release.

–RELENZA is inhaled into the lungs, the primary site of viral replication.

–RELENZA helps stop replication and shortens the course of influenza A & B.

–Side effects are comparable to placebo, with no adverse events >3% in over 2,500 patients.

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Slide 13

Clinical pharmacology

Activity of RELENZA® (zanamivir for inhalation) is concentrated in the lungs*

- Low oral bioavailability (~2%)
- Low systemic bioavailability (~10%)
- Rapidly excreted, renally unchanged
- No interaction with trivalent inactivated influenza vaccine
- Low potential for drug-drug interactions
- Generally well tolerated

* Data from 22 trials, results in 490/654 subjects

Clinical pharmacology[12]

Activity of RELENZA is concentrated in the lungs. In 22 clinical trials in which RELENZA was administered to 654 subjects, the following results were reported in 490 subjects:

–Low oral bioavailability (~2%) and systemic bioavailability (4%-17%).

–Renally excreted as unchanged drug; a single dose is excreted within 24 hours.

–No interference with the antibody response to the influenza vaccine.

–Low potential for drug-drug interactions.

–Does not affect cytochrome P450 isoenzymes.

–Generally well tolerated in clinical trials.

–No identified safety issues from administration of RELENZA in safety study in which doses of 1,200 mg/day IV were administered.

References: 12. Data on file, Glaxo Wellcome, Inc., Research Triangle Park, NC. **13.** Cass LMR, Brown J, Pickford M, et al. Pharmacoscintigraphic evaluation of lung deposition of inhaled zanamivir in healthy volunteers. *Clinical Pharmacokinetics.* 36(suppl.1):21-31,1999.

Slide 14

Delivers antiviral action to the primary site of viral replication

Post-dosing scan of deposition of RELENZA® (zanamivir for inhalation) at 4 minutes

RELENZA
Higher concentrations of RELENZA

The correlation between scintigraphic imaging and clinical results has not been established

Delivers antiviral action to the primary site of viral replication

After inhalation of a single technetium-radiolabeled 10-mg dose of RELENZA by 12 healthy adult volunteers, two-dimensional scintigraphic imaging scans of the lungs showed that[13]:

–RELENZA was distributed to the trachea, bronchi, bronchioles, and alveoli.

–Estimated concentration was 1,868 ng/mL and far exceeded the viral IC_{50} of strains of influenza observed in clinical studies.

–The correlation between scintigraphic imaging and clinical results has not been established.

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Slide 15

Delivers concentrations exceeding viral IC_{50}

- Deposition in the upper and lower airways (~1,400 times the EIC_{50}) far exceeds the viral IC_{50} of influenza A and B
- The correlation between scintigraphic imaging and clinical results has not been established

Delivers concentrations exceeding the viral IC_{50}[13]

Deposition of RELENZA in the upper and lower airways (~1,400 times the EIC_{50}) achieves levels that far exceed the viral IC_{50} and IC_{90} of influenza A and B.

–The correlation between scintigraphic imaging and clinical results has not been established.

Slide 16

RELENZA® (zanamivir for inhalation): No treatment-emergent resistance in clinical trials

- No treatment-emergent resistance has been observed in completed and ongoing clinical trials in over 8,500 patients
- Insufficient information is available to characterize the risk of emergence of zanamivir resistance in clinical use
- Local application with low systemic exposure
- One case of resistance reported in an immunocompromised pediatric patient

RELENZA: No treatment-emergent resistance in clinical trials

No treatment-emergent resistance has been observed in completed and ongoing clinical trials in over 8,500 patients.

–Insufficient information is available to characterize the risk of emergence of zanamivir resistance in clinical use.

–RELENZA has local application with low systemic exposure.

–One case of resistance was reported in an immunocompromised pediatric patient. This pediatric patient received ribavirin for 2 weeks prior to being given an investigational form (by nebulizer) of RELENZA in an emergency, compassionate-use situation.

References: 12. Data on file, Glaxo Wellcome, Inc., Research Triangle Park, NC. **13.** Cass LMR, Brown J, Pickford M, et al. Pharmacoscintigraphic evaluation of lung deposition of inhaled zanamivir in healthy volunteers. *Clinical Pharmacokinetics.* 1999;36(suppl.1):21-31.

RELENZA®

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Slide 17

As versatile as your patient population

- RELENZA® (zanamivir for inhalation) is indicated for treatment of uncomplicated acute illness due to influenza virus in adults and adolescents 12 years and older
- Patients judged to be in population groups most likely to benefit include:
  - Patients with higher baseline temperatures (38.2°C/100°F)
  - Patients judged to have more severe symptoms

As versatile as your patient population

RELENZA is indicated for the treatment of uncomplicated acute illness due to influenza virus in adults and adolescents 12 years and older.

Patients judged to be in population groups most likely to benefit include:

–Patients with higher baseline temperatures (38.2°C/100°F or more);

–Patients judged to have more severe symptoms.

RELENZA may be appropriate for indicated patients who wish to shorten the misery of influenza, so they can get back to the things that matter most.

Slide 18

Phase III trials: symptom improvement

- Efficacy was evaluated in large-scale, placebo-controlled, multicenter trials on three continents during their respective influenza seasons
- Primary endpoint was time to improvement of major symptoms
  - No fever or feverishness;
  - Self-assessment of "none" or "mild" for headache, myalgia, cough, and sore throat;
  - Symptom relief that was consistently maintained for 24 hours.

Phase III trials: symptom improvement

RELENZA 10 mg inhaled twice daily was studied in placebo-controlled trials in North America, the Southern Hemisphere, and Europe during their respective flu seasons.

The primary endpoint was time to improvement of major symptoms, defined as:

–No fever or feverishness;

–Self-assessment of "none" or "mild" for headache, myalgia, cough, and sore throat;

–Symptom relief that was consistently maintained for 24 hours.

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Slide 19

Reduced the duration of major symptoms

- In North American phase II and III studies, RELENZA® (zanamivir for inhalation) shortened the course of the flu by up to 1 day[14–16]
- In a Southern Hemisphere trial, RELENZA shortened the course of the flu by 1.5 days[17]
- Additional evidence of efficacy was provided by a study conducted in Europe[18]
- Across all phase III studies, 89% of patients had influenza A and 11% had influenza B

Reduced the duration of major symptoms in clinical trials

Principal phase III studies enrolled 1,588 patients with uncomplicated influenza-like illness within 2 days of symptom onset.

RELENZA reduced the duration of illness in adults and adolescents 12 years of age and older:

–In North American phase II and III studies, RELENZA shortened the course of the flu by up to 1 day.[14-16]

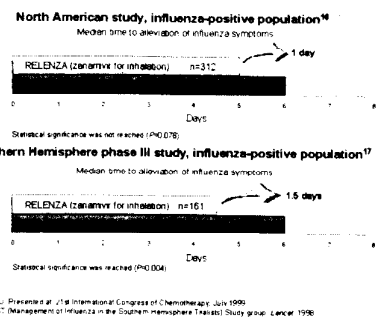
–In a Southern Hemisphere phase II study, RELENZA shortened the course of the flu by 1.5 days.[17]

–Additional evidence of efficacy was provided by a study conducted in Europe.[18]

References: 14. Hayden FG, Osterhaus ADME, Treanor JJ et al. Efficacy and safety of the neuraminidase inhibitor zanamivir in the treatment of influenza virus infections. *N Eng J Med.* 1997;337:874-880. **15.** Monto AS, Fleming DM, Henry D, de Groot R, Makela M, Klein T, Elliot M, Keene ON, Man CY. Efficacy and safety of the neuraminidase inhibitor zanamivir in the treatment of influenza A and B virus infections. *J Infect Dis.* 1999;180:254-61. **16.** Lalezari J, Klein T, Stapleton J, Elliott M, Flack N, Keene O. Presented at: 21st International Congress of Chemotherapy; July 4-7, 1999; Birmingham, England. **17.** The MIST (Management of Influenza in the Southern Hemisphere Trialists) Study Group. Randomised trial of efficacy and safety of inhaled zanamivir in treatment of influenza A and B virus Infections. *Lancet.* 1998;352:1877-1881. **18.** Fleming D, Makela M, Pauksens K, Man CY, Webster A, Keene ON. Presented at IDSA; Denver, CO. September 11-15, 1998.

Slide 20

Shortened the course of the flu



16. Lalezari J. Presented at: 21st International Congress of Chemotherapy; July 1999.
17. The MIST (Management of Influenza in the Southern Hemisphere Trialists) Study group. Lancet 1998.

RELENZA shortened the course of the flu

In North American phase II and phase III studies, RELENZA shortened the duration of the flu by up to 1 day.[14-16]

In the phase III North American study, RELENZA shortened the duration of the flu by 1 day.[16]

–Statistical significance was not reached (P=0.078) in this study.

In a Southern Hemisphere study, RELENZA shortened the duration of flu by 1.5 days[17]:

–Statistical significance was reached (P=0.004) in this study.

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Slide 21

Side effects comparable to placebo with no adverse events >3% in over 2,500 patients

Summary of Adverse Events ≥1.5% Incidence During Treatment

Adverse Event	RELENZA 10 mg b.i.d. (n=1,132)	placebo lactose vehicle (n=1,520)
Headaches	2%	3%
Diarrhea	3%	4%
Nausea	3%	3%
Vomiting	1%	2%
Nasal signs and symptoms	2%	3%
Bronchitis	2%	3%
Cough	2%	3%
Sinusitis	3%	2%
Ear, nose, and throat infections	2%	2%
Dizziness	2%	<1%

RELENZA has a side-effect profile comparable to placebo with no adverse events >3% in over 2,500 patients

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

Slide 22

Delivers a very favorable safety profile

- No adverse events >3% in over 2,500 patients
- No clinically significant drug interactions expected, based on data from in vitro studies
- CNS, gastrointestinal, and other systemic effects are comparable to placebo
- No need to take with food to reduce the incidence or severity of side effects

RELENZA delivers a very favorable safety profile

In clinical trials with RELENZA, side effects were comparable to placebo with no adverse events >3% in over 2,500 patients.

No clinically significant drug interactions are expected, based on data from in vitro studies.

CNS, gastrointestinal, and other systemic effects are comparable to placebo.

There is no need to take RELENZA with food to reduce the incidence or severity of side effects.

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Slide 23

Delivers a very favorable product profile

- Only 4% to 17% of the inhaled dose is systemically absorbed
- RELENZA® (zanamivir for inhalation) is not metabolized
- RELENZA has limited plasma protein binding (<10%)
- No interference with influenza vaccine
- Safety and efficacy have not been established in high-risk patients with underlying medical conditions, and this drug may cause bronchospasm and/or a decline in lung function in patients with severe or decompensated COPD or asthma

RELENZA delivers a very favorable product profile

Pharmacokinetics studies indicate that only 4% to 17% of the inhaled dose is systemically absorbed.

–RELENZA is not metabolized.

–No interference with P450 liver enzymes.

–RELENZA has limited plasma protein binding (<10%).

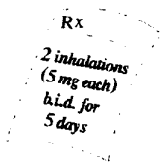
–No interference with antibody response to trivalent inactivated influenza vaccine.

–Safety and efficacy have not been established in high-risk patients with underlying medical conditions, and this drug may cause bronchospasm and/or a decline in lung function in patients with severe or decompensated COPD or asthma.

Slide 24

Convenient dosing schedule

- Breath-activated, nonaerosol oral DISKHALER®
- For maximum benefit, therapy with RELENZA® (zanamivir for inhalation) should be initiated as soon as possible and within 2 days of onset of symptoms



RELENZA has a convenient dosing schedule

RELENZA is delivered via the breath-activated, nonaerosol oral DISKHALER®.

The dosing schedule is two inhalations (2 x 5 mg) twice daily—approximately 12 hours apart—for 5 days.

For maximum benefit, therapy with RELENZA should be initiated as soon as possible and within 2 days of onset of symptoms.

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Slide 25

Logical treatment modality
DISKHALER® delivery system

Patients should be instructed in the use of the DISKHALER, including a demonstration, whenever possible.

DISKHALER® delivery system

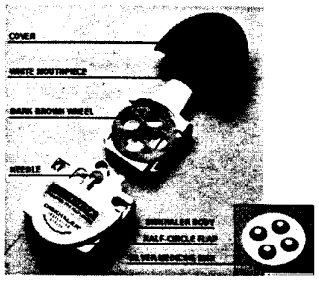
RELENZA delivers inhaled antiviral action to fight an airborne respiratory disease.

The DISKHALER system is breath-activated and nonaerosol.

Patients should be instructed in the use of the DISKHALER, including a demonstration, whenever possible.

Slide 26

Parts of the DISKHALER®



Loading the medicine into the DISKHALER®

To use the DISKHALER, the patient should follow these steps:

–Remove the blue cover and check inside the mouthpiece to ensure that it is free of foreign objects.

–Pull the white mouthpiece by the edges to fully extend the white tray.

–Once the tray is completely extended, press in the raised ridges on each side at the same time and remove the tray from the DISKHALER body.

–Place one silver medicine disk on the wheel, flat side up. The 4 blisters should fall neatly in the holes, allowing the tray to be pushed all the way back.

Now, the DISKHALER is loaded and ready for use.

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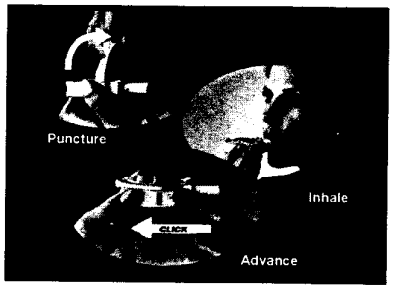
Slide 27

Using the DISKHALER®



Puncture, Inhale, and Advance

The DISKHALER only punctures one blister at time, so that patients can inhale the correct amount. To take the medication, the patient should:

–Keep the DISKHALER level, lift the flap all the way up to puncture the blister, then click it back down. It is important they keep the DISKHALER level to avoid spilling the contents once the blister is punctured.

–Exhale completely and then inhale steadily and deeply to ensure greatest deposition in airways and lungs.

To advance to the next blister, pull the mouthpiece to extend the white tray (without removing it), then push it back in until the DISKHALER clicks.

To take the next inhalation, simply repeat the puncture and inhale steps.

Slide 28

Important information

- RELENZA® (zanamivir for inhalation) is indicated for the treatment of uncomplicated acute illness due to influenza virus in adults and adolescents 12 years and older who have been symptomatic for no more than 2 days.
- For maximum benefit, therapy with RELENZA should be initiated as soon as possible and within 2 days of symptom onset. There are no data on the effectiveness of treatment with RELENZA when initiated more than 2 days after the onset of signs or symptoms.

Important information

RELENZA is indicated for the treatment of uncomplicated acute illness due to influenza virus in adults and adolescents 12 years and older who have been symptomatic for no more than 2 days.

For maximum benefit, therapy with RELENZA should be initiated as soon as possible and within 2 days of symptom onset. There are no data on the effectiveness of treatment with RELENZA when initiated more than 2 days after the onset of signs or symptoms.

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Slide 29

Other prescribing considerations

Use of RELENZA® (zanamivir for inhalation) should not affect the evaluation of patients for annual influenza vaccination in accordance with CDC guidelines

Other prescribing considerations

Use of RELENZA should not affect the evaluation of patients for annual influenza vaccination in accordance with CDC guidelines.

Slide 30

The first inhaled antiviral that fights both influenza A & B at the primary site of viral replication

- Delivers neuraminidase inhibition directly to the lungs
- Shortens the duration of major symptoms of flu
- Has an adverse event profile comparable to placebo
- Demonstrates efficacy in adults and adolescents 12 years of age and older
- Can initiate therapy up to 2 days after symptom onset
- Is appropriate for a wide age range of patients

The most commonly reported side effects vs. placebo were diarrhea (3% vs. 4%), nausea (3% vs. 3%), and sinusitis (3% vs. 2%)

The first inhaled antiviral that fights both influenza A & B at the primary site of viral replication

–The breath-activated, nonaerosol DISKHALER® delivers neuraminidase inhibition directly to the lungs.

–Antiviral activity shortens the duration of major flu symptoms.

–RELENZA has a very favorable safety profile with adverse events comparable to placebo.

–Efficacy was demonstrated in adults and adolescents 12 years of age and older.

–Therapy should be initiated within 2 days of symptom onset.

–RELENZA is appropriate for indicated patients who wish to shorten the misery of flu and get back to what matters most.

The most commonly reported side effects vs. placebo were diarrhea (3% vs. 4%), nausea (3% vs. 3%), and sinusitis (3% vs. 2%).

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RELENZA is indicated for the treatment of uncomplicated acute illness due to influenza virus in adults and adolescents 12 years and older who have been symptomatic for no more than 2 days.

The safety and efficacy of RELENZA have not been established in patients with high-risk underlying medical conditions. In patients with severe or decompensated COPD or asthma, this drug may cause bronchospasm and/or a decline in lung function. These patients should have fast-acting inhaled bronchodilators available.

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Please consult accompanying complete Prescribing Information.

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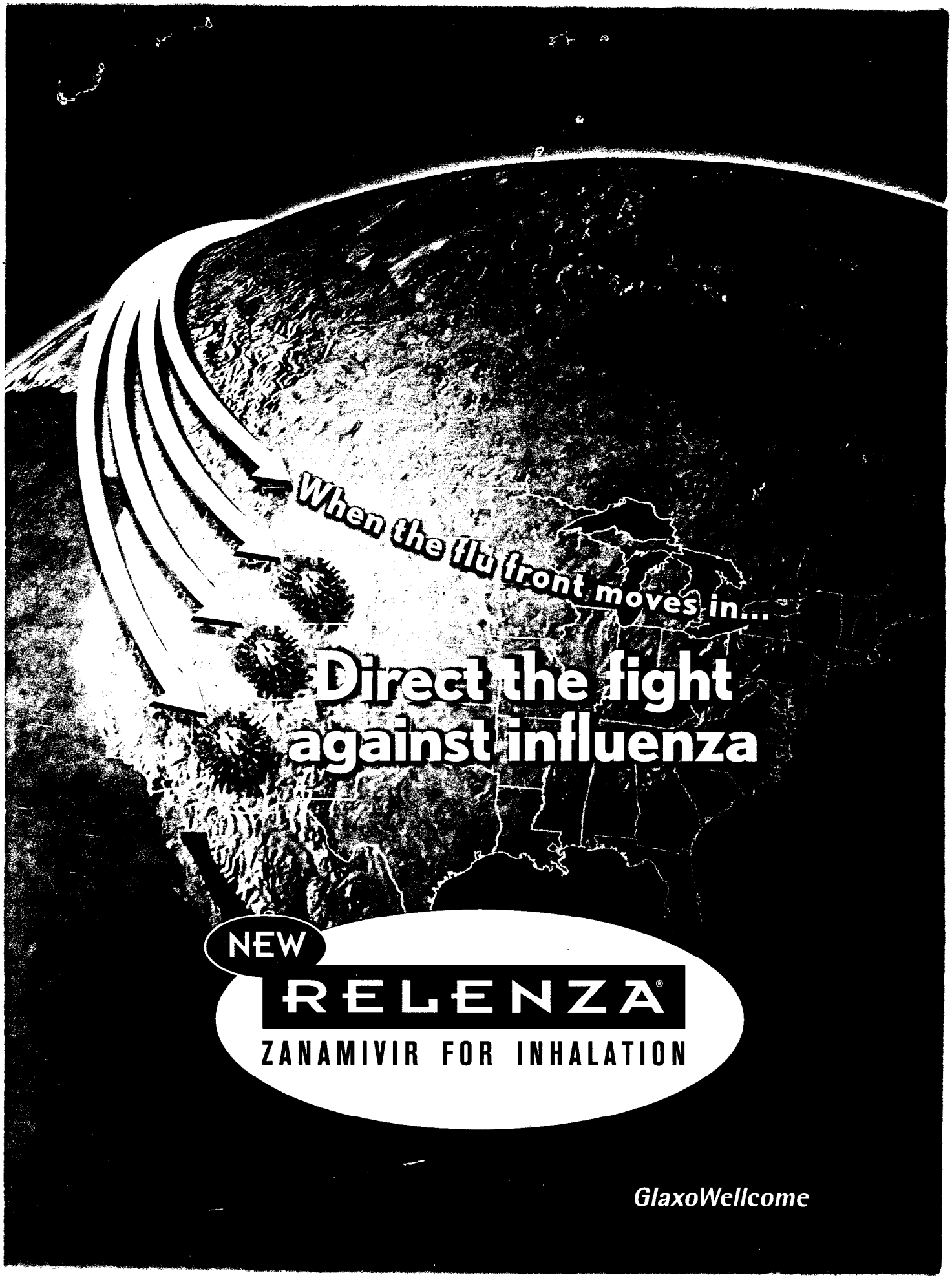
GlaxoWellcome
Glaxo Wellcome Inc.
Research Triangle Park, NC 27709
Web site: www.glaxowellcome.com


When the flu front moves in...
Direct the fight against influenza
NEW
RELENZA®
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GlaxoWellcome

The safety and efficacy of RELENZA have not been established in patients with high-risk underlying medical conditions, and this drug may cause bronchospasm and/or a decline in lung function in patients with severe or decompensated COPD or asthma. These patients should have fast-acting inhaled bronchodilators available.

Please see back for brief summary of full Prescribing Information for RELENZA.

help move influenza out

New, inhaled RELENZA delivers antiviral action to the lungs and shortens the course of the flu

- **Influenza is an acute respiratory infection** primarily restricted to the lungs and airways[1]
- **Demonstrated efficacy in a wide age range of patients–** adults and adolescents 12 years of age and older
- **Very favorable safety profile** with side effects comparable to placebo—no adverse events >3% in over 2,500 patients
- **Local application with low systemic exposure**
- **For maximum benefit, therapy with RELENZA should be initiated as soon as possible and within 2 days of symptom onset**

RELENZA is indicated for the treatment of uncomplicated acute illness due to influenza virus in adults and adolescents 12 years and older who have been symptomatic for no more than 2 days. The most commonly reported side effects vs. placebo were diarrhea (3% vs. 4%), nausea (3% vs. 3%), and sinusitis (3% vs. 2%). Patients should be instructed in the use of the delivery system, including a demonstration whenever possible.

NEW

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Focus on the lungs to fight flu A & B

NEW

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Reference: 1. Betts RF. Influenza virus. In: Mandell GL, Bennett JE, Dolin R, eds. *Principles and Practice of Infectious Diseases*. 4th ed. New York, NY: Churchill Livingstone; 1995:1546–1567.

BRIEF SUMMARY

RELENZA®
(zanamivir for inhalation)

For Oral Inhalation Only
For Use with the DISKHALER® Inhalation Device

The following is a brief summary only; see full prescribing information for complete product information.

CONTRAINDICATIONS: RELENZA is contraindicated in patients with a known hypersensitivity to any component of the formulation.

PRECAUTIONS:

General: Patients should be instructed in the use of the delivery system. Instructions should include a demonstration whenever possible. Patients should read and follow carefully the Patient Instructions for Use accompanying the product. Effective and safe use of RELENZA requires proper use of the DISKHALER to inhale the drug.

There is no evidence for efficacy of zanamivir in any illness caused by agents other than influenza virus A and B. Data on treatment of influenza B are limited (see INDICATIONS AND USAGE: Description of Clinical Studies section of full prescribing information).

No data are available to support safety or efficacy in patients who begin treatment after 48 hours of symptoms.

Safety and efficacy of repeated treatment courses have not been studied.

Patients with Underlying Respiratory Disease: Safety and efficacy have not been demonstrated in patients with underlying chronic pulmonary disease. In particular, this product has not been shown to be effective, and may carry risk, in patients with severe or decompensated chronic obstructive pulmonary disease or asthma. 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 1 study. In interim results from an ongoing treatment study in patients with acute influenza-like illness superimposed on underlying asthma or chronic obstructive pulmonary disease, more patients on zanamivir than on placebo experienced greater than 20% decline in FEV_1 or peak expiratory flow rate. Some patients with underlying respiratory disease may experience bronchospasm and/or decline in lung function when treated with zanamivir. Any patient who develops bronchospasm or decline in lung function should stop the drug. Patients with underlying respiratory disease should be instructed to have a fast-acting inhaled bronchodilator available when treated with zanamivir.

Prevention of Influenza: Use of zanamivir should not affect the evaluation of individuals for annual influenza vaccination in accordance with guidelines of the Centers for Disease Control and Prevention Advisory Committee on Immunization Practices. Safety and efficacy of zanamivir have not been established for prophylactic use of zanamivir to prevent influenza.

Limitations of Populations Studied: Safety and efficacy have not been demonstrated in patients with high-risk underlying medical conditions (see INDICATIONS AND USAGE: Description of Clinical Studies section of full prescribing information). 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.

Information for Patients: 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.

Patients should be advised to finish the entire 5-day course of treatment even if they start to feel better sooner.

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.

Patients with asthma or chronic obstructive pulmonary disease should be advised of the potential risk of bronchospasm with zanamivir, should have a fast-acting inhaled bronchodilator available, and should stop zanamivir and contact their physician promptly if they experience worsening respiratory symptoms. Patients scheduled to take inhaled bronchodilators at the same time as RELENZA should be advised to use their bronchodilators before taking RELENZA.

Drug Interactions: No clinically significant pharmacokinetic drug interactions are predicted based on data from in vitro studies.

Carcinogenesis, Mutagenesis, and 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 per 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-per-day IV dose, AUC values ranged between 142 and 199 mcg-h/mL (>300 times the human exposure at the proposed clinical dose).

Pregnancy: Pregnancy Category B. 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. Pre- and post-natal developmental studies were performed in rats (dosed from day 16 of pregnancy until litter day 21 to 23). In all studies, intravenous (1, 9, and 90 mg/kg per day) instead of the inhalational route of drug administration was used. No malformations, maternal toxicity, or embryotoxicity were observed in pregnant rats or rabbits and their fetuses. Because of insufficient blood sampling timepoints in both rat and rabbit reproductive toxicity studies, AUC values were not available. However, in a subchronic study in rats at the 90-mg/kg-per-day IV dose, the AUC values were greater than 300 times the human exposure at the proposed clinical dose.

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.

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.

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.

Pediatric Use: Safety and effectiveness in pediatric patients below 12 years of age have not been established. In the three principal phase 3 treatment 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.

Geriatric Use: Of the total number of patients in 6 clinical treatment studies of RELENZA, 59 were 65 and over, while 24 were 75 and over. No overall differences in safety or effectiveness were observed between these subjects 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.

ADVERSE REACTIONS: 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 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

Adverse Event	RELENZA		Placebo (Lactose Vehicle†) (n = 1520)
	10 mg b.i.d. Inhaled (n = 1132)	All Dosing Regimens* (n = 2289)	
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, & 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.

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

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 3 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.

See PRECAUTIONS for safety information in patients with underlying respiratory disease.

OVERDOSAGE: There have been no reports of overdosage from administration of RELENZA. Doses of zanamivir up to 64 mg/day have been administered by nebulizer. Additionally, doses of up to 1200 mg/day for 5 days have been administered intravenously. Adverse effects were similar to those seen in clinical studies at the recommended dose.

GlaxoWellcome

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US Patent Nos. 4,627,432; 4,778,054; 4,811,731; 5,360,817; 5,648,379; 5,035,237; Des. 379,506

When the flu front moves in...

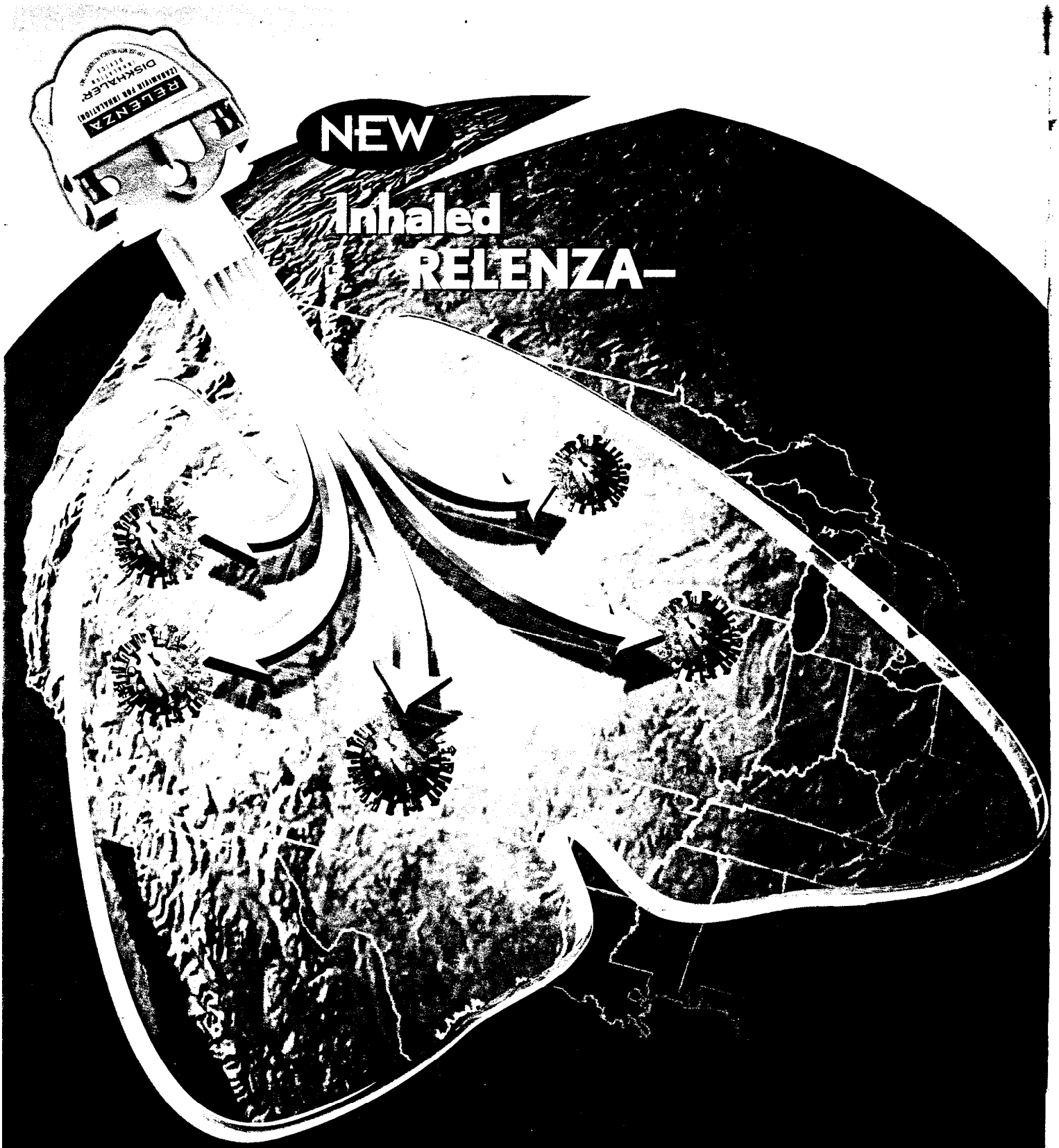
Direct the fight against influenza

NEW

RELENZA®

ZANAMIVIR FOR INHALATION

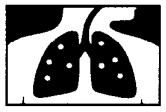
GlaxoWellcome



RELENZA is indicated for the treatment of uncomplicated acute illness due to influenza virus in adults and adolescents 12 years and older who have been symptomatic for no more than 2 days.

Goes to the lungs to help move influenza out

The first and only inhaled antiviral that fights both influenza A & B—directly at the primary site of viral replication

- Often perceived as a systemic disease, influenza is actually an acute respiratory infection primarily restricted to the lungs and airways[1]
  - —Viral replication occurs in the respiratory epithelium 
  - —Neuraminidase enzymes facilitate replication by aiding the release of mature virions from infected cells

The first viral neuraminidase inhibitor

- Inhaled RELENZA delivers antiviral action to the respiratory tract—the primary site of viral replication 
- Helps stop viral replication and shorten the course of the flu

NEW

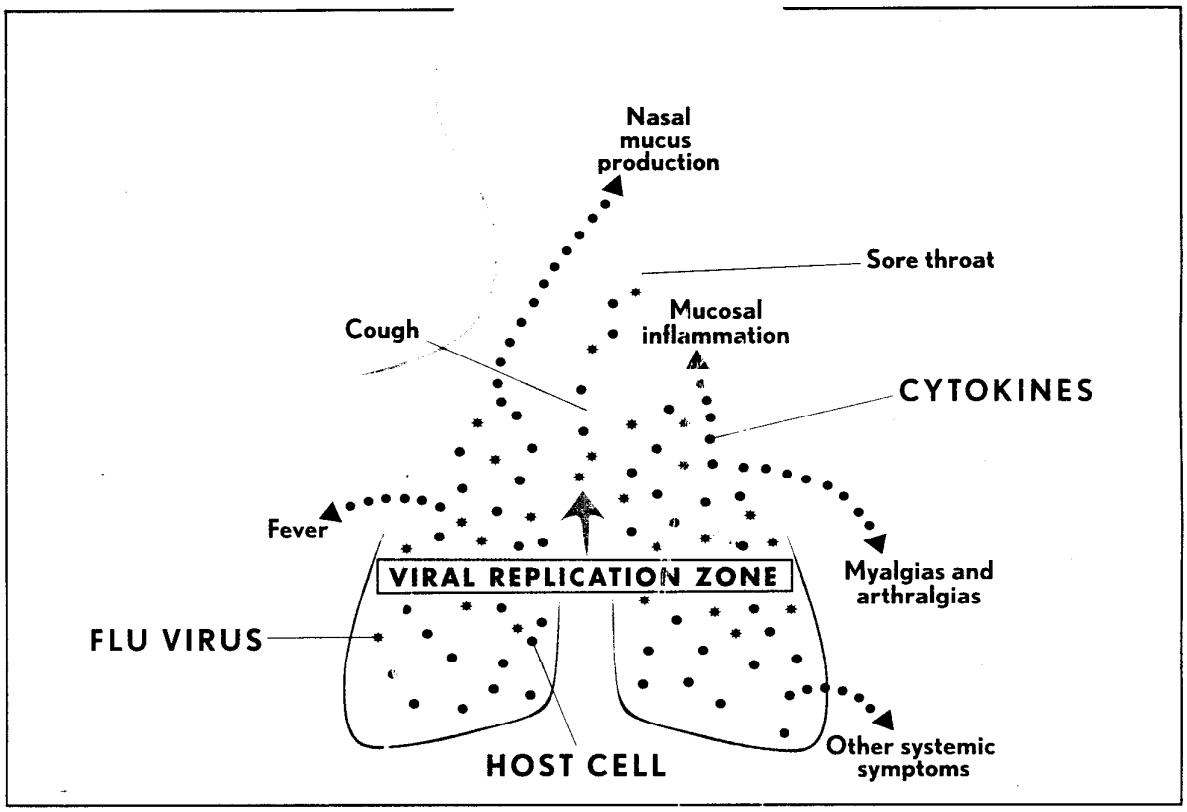
RELENZA®

ZANAMIVIR FOR INHALATION

The direct way to fight flu A & B

Please consult complete Prescribing Information for RELENZA on last pages.

New Inhaled RELENZA–
Fight an airborne respiratory disease...



Spread by airborne droplets

- Onset initially characterized by fever and upper respiratory symptoms, e.g., **sore throat** and **cough**[1]

CYTOKINES–
the culprits of "systemic" symptomatology[2,3]

- Cytokine release causes systemic symptoms, e.g., high fever, myalgia/arthralgia, and loss of appetite
- Host defenses lead to mucosal inflammation

...with inhaled antiviral action

Breath-activated delivery of RELENZA reaches the Viral Replication Zone in the lungs

- Inhaled RELENZA delivers antiviral activity to the primary site of viral replication
- Local application with low systemic exposure
- No treatment-emergent resistance in uncomplicated influenza seen in clinical trials
  - —Insufficient information is available to characterize the risk of emergence of zanamivir resistance in clinical use

NEW

RELENZA®

ZANAMIVIR FOR INHALATION

The direct way to fight flu A & B

Please consult complete Prescribing Information for RELENZA on last pages.