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.

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.

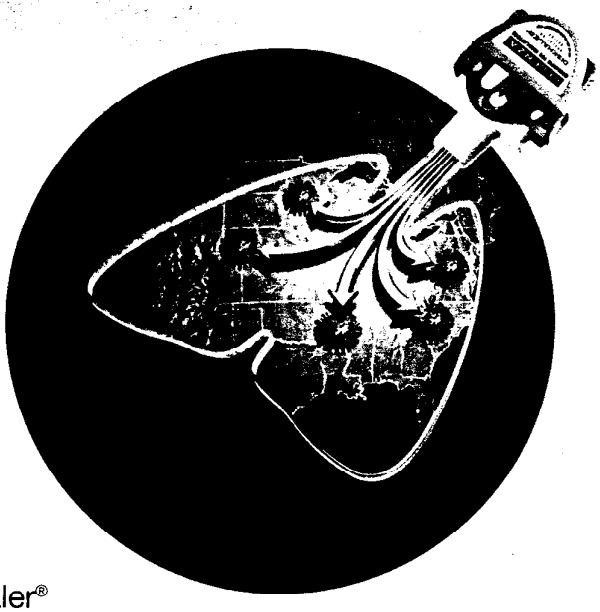
GlaxoWellcome
Glaxo Wellcome Inc.
Research Triangle Park, NC 27709

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-728

New Inhaled RELENZA–

The first and only inhaled antiviral that fights both influenza A & B– directly at the primary site of infection



- Breath-activated, nonaerosol Diskhaler® delivers neuraminidase inhibition to the lungs
- Shortens the duration of major symptoms of flu
- Very favorable safety profile with side effects comparable to placebo—no adverse events >3% in over 2,500 patients
- Demonstrated efficacy in a wide age range of patients—adults and adolescents 12 years of age and older
- Up to 2 days to initiate therapy after symptom onset

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

NEW

RELENZA®

ZANAMIVIR FOR INHALATION

The direct way to fight flu A & B

Please consult complete Prescribing Information for RELENZA on last pages.

References: 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. **2.** Madoff LC, Kasper DL. Introduction to infectious diseases: host-parasite interaction. In: Fauci AS, Braunwald E, Isselbacher KJ, eds. *Harrison's Principles of Internal Medicine.* New York, NY: McGraw-Hill; 1998:749-754. **3.** Hayden FG, Fritz RS, Lobo MC, Alvord WG, Strober W, Straus SE. Local and systemic cytokine responses during experimental human influenza A virus infection: relation to symptom formation and host defense. *J Clin Invest.* 1998;101:643–649. **4.** 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. **5.** The MIST (Management of Influenza in the Southern Hemisphere Trialists) Study group. Randomised trial of influenza A and B virus infections. *Lancet.* December 12, 1998;352:1877–1881.

Printed in USA. RLZ046R0 August 1999

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Glaxo Wellcome Inc.
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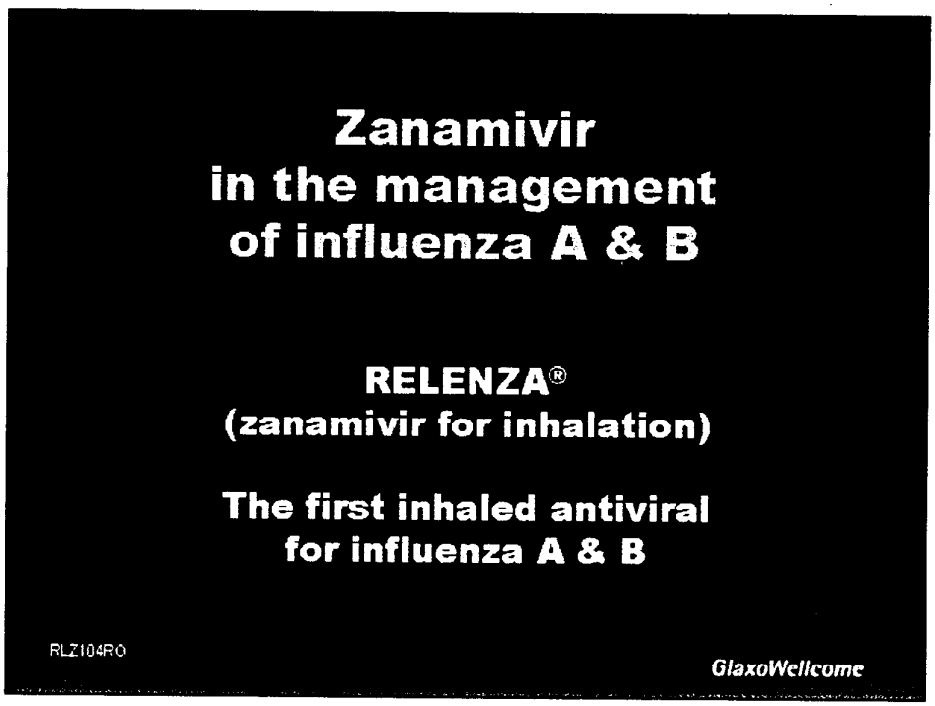
Web site: www.glaxowellcome.com

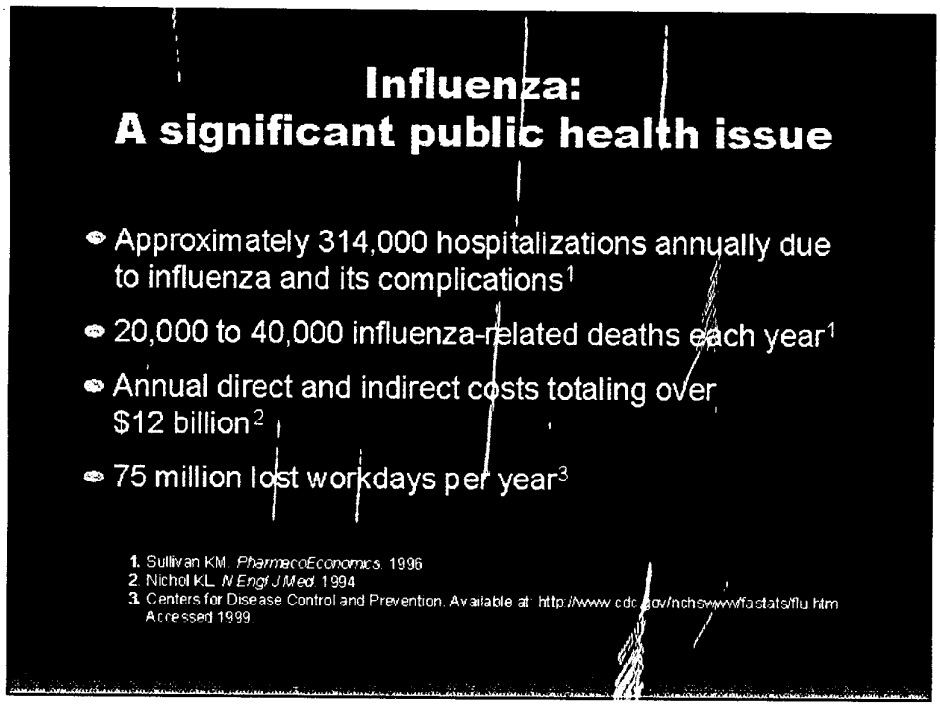


Zanamivir in the management of influenza A & B

This presentation focuses on RELENZA® (zanamivir for inhalation) 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.

RLZ104RO



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:

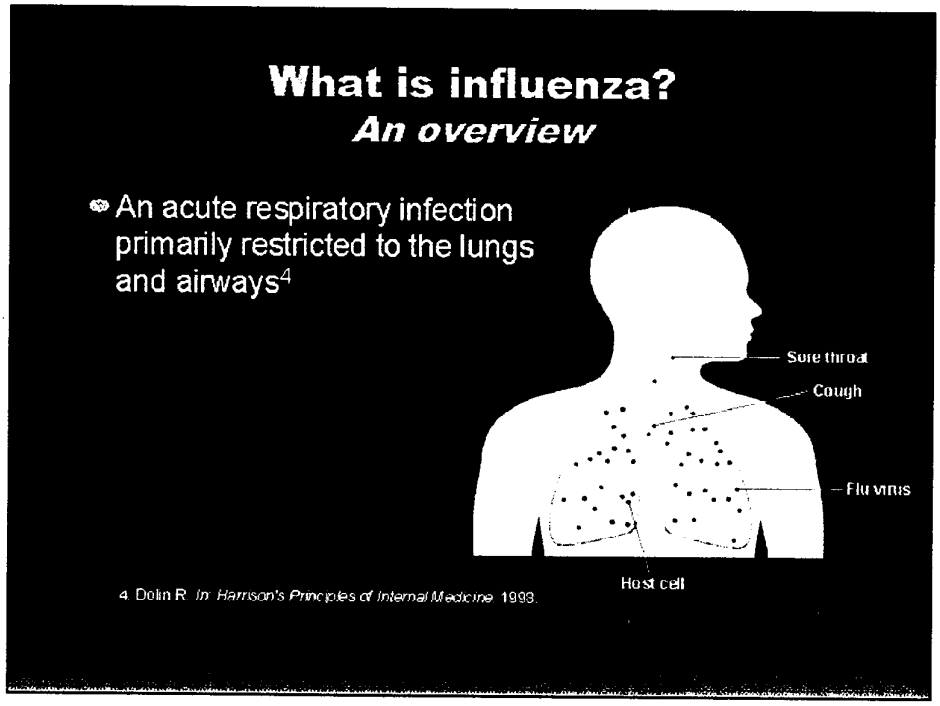
–Approximately 303 million days of restricted activity.[3]

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

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.



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]:

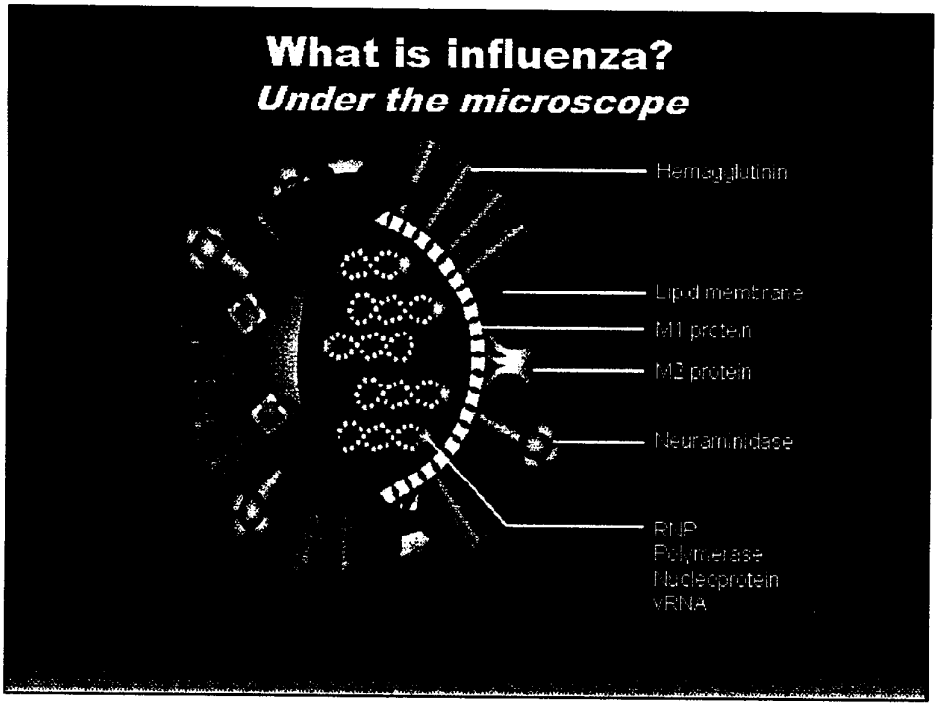
–Onset is typically abrupt and characterized by fever and upper respiratory manifestations such as sore throat and cough.

–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.

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.



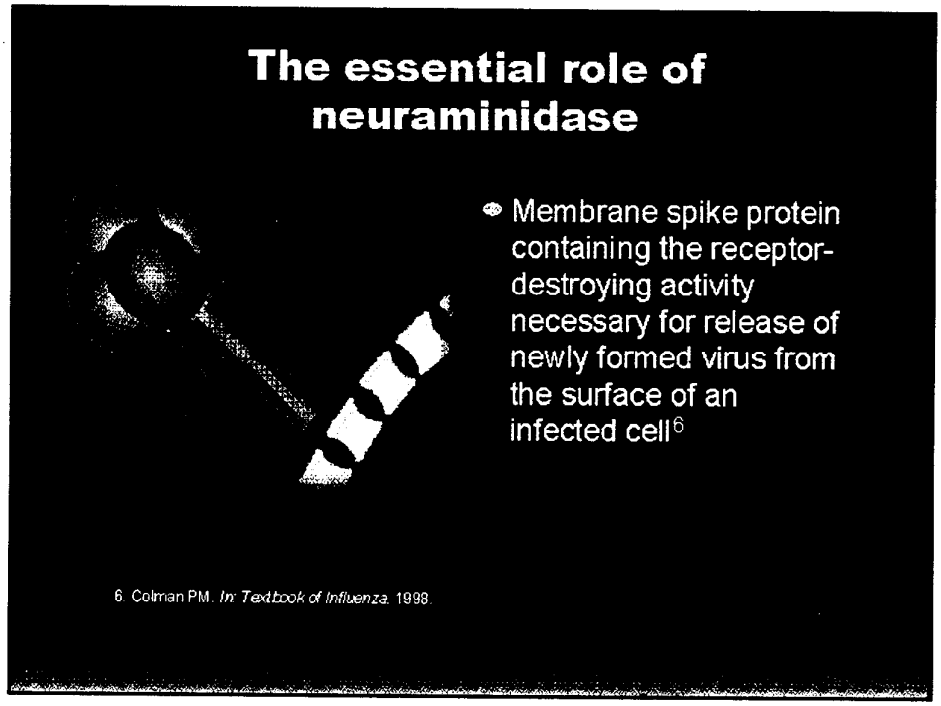
The influenza virus: under the microscope[5]

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.

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.

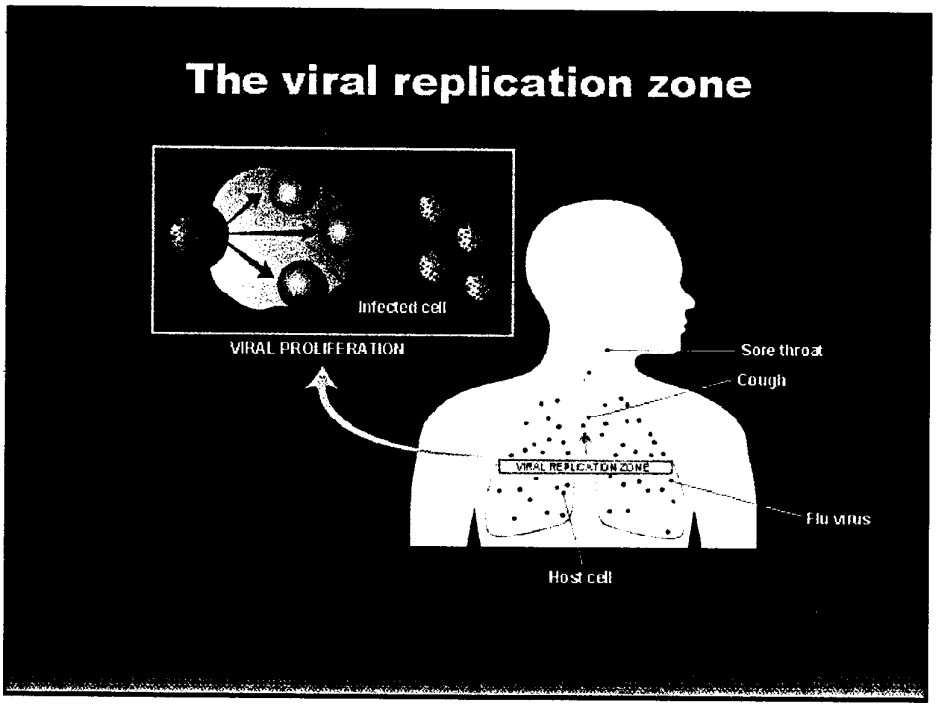


The essential role of neuraminidase[6]

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.

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.

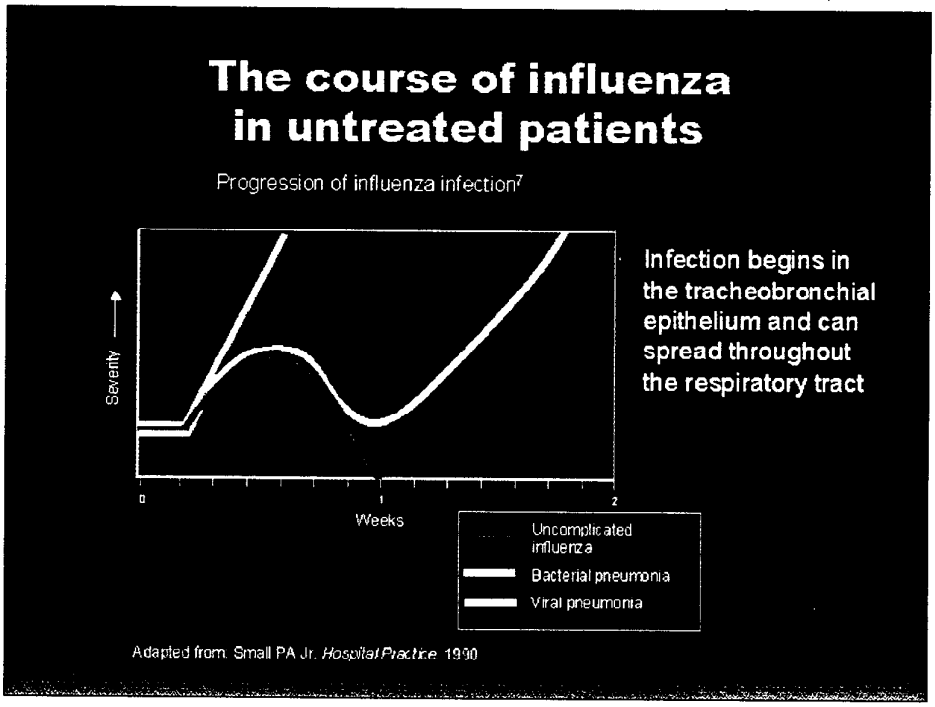


The viral replication zone[5]

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.

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.



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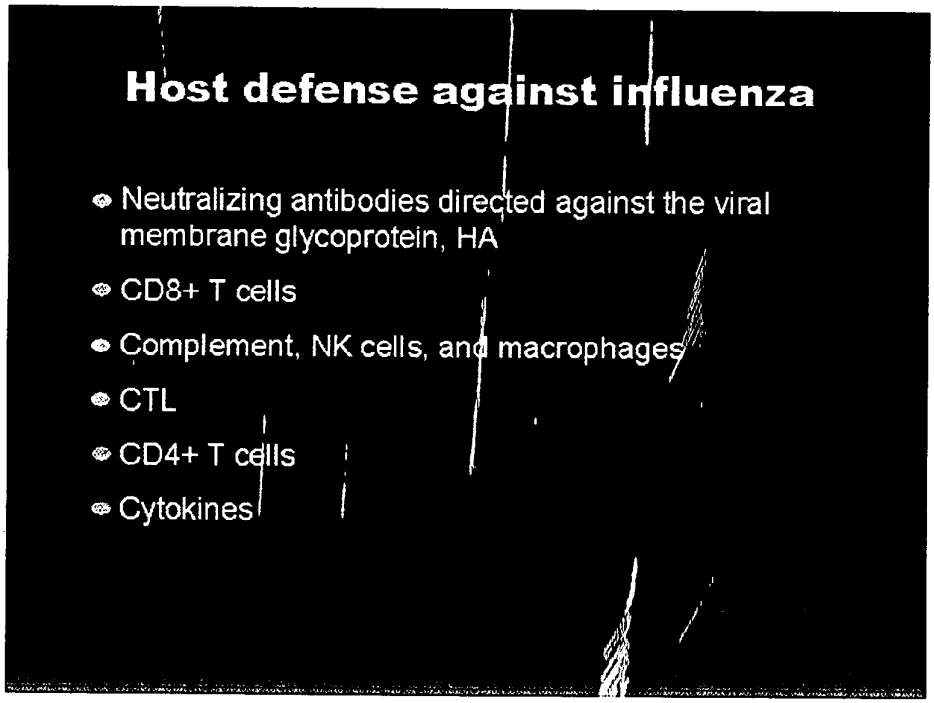
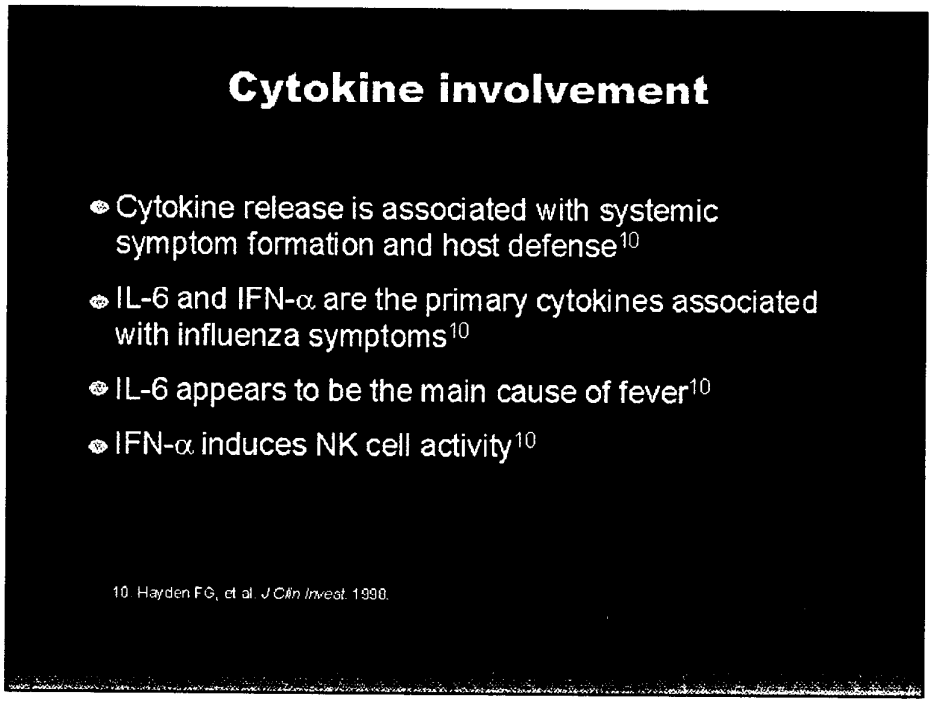


Host defense against influenza[8,9]

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.

8. Thomas DB. Antibody-Mediated Immunity. In: Nicholson KG, Webster RG, Hay AJ. *Textbook of Influenza*. London, England: Blackwell Science; 1998:267-277.

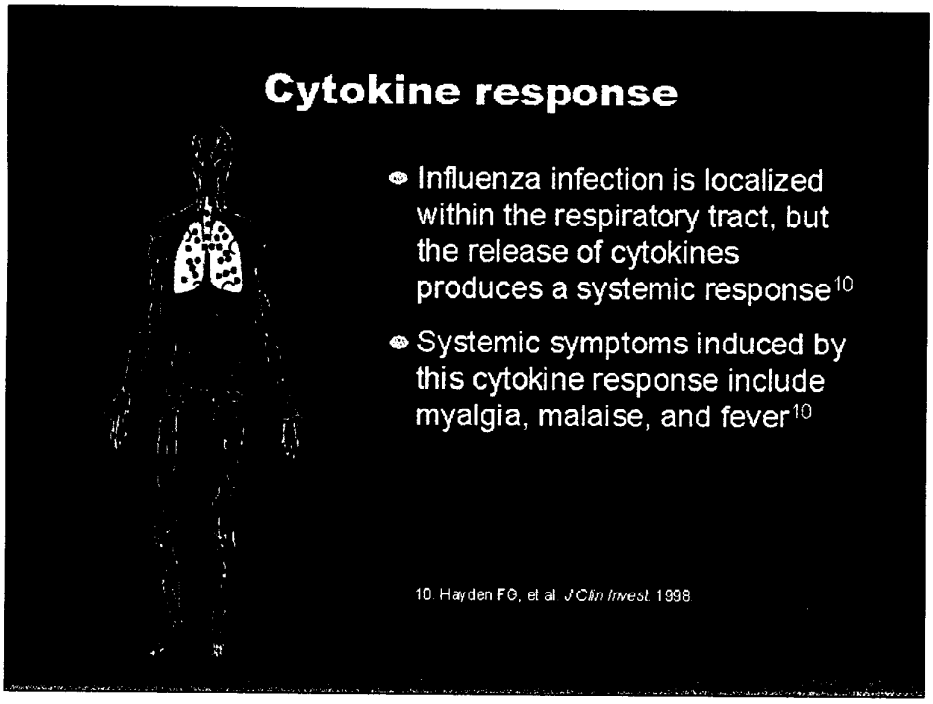
9. Stevenson PG and Doherty PC. Cell-Mediated Immune Response to Influenza Virus. In: Nicholson KG, Webster RG, Hay AJ. *Textbook of Influenza*. London, England: Blackwell Science; 1998:278-287.



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.

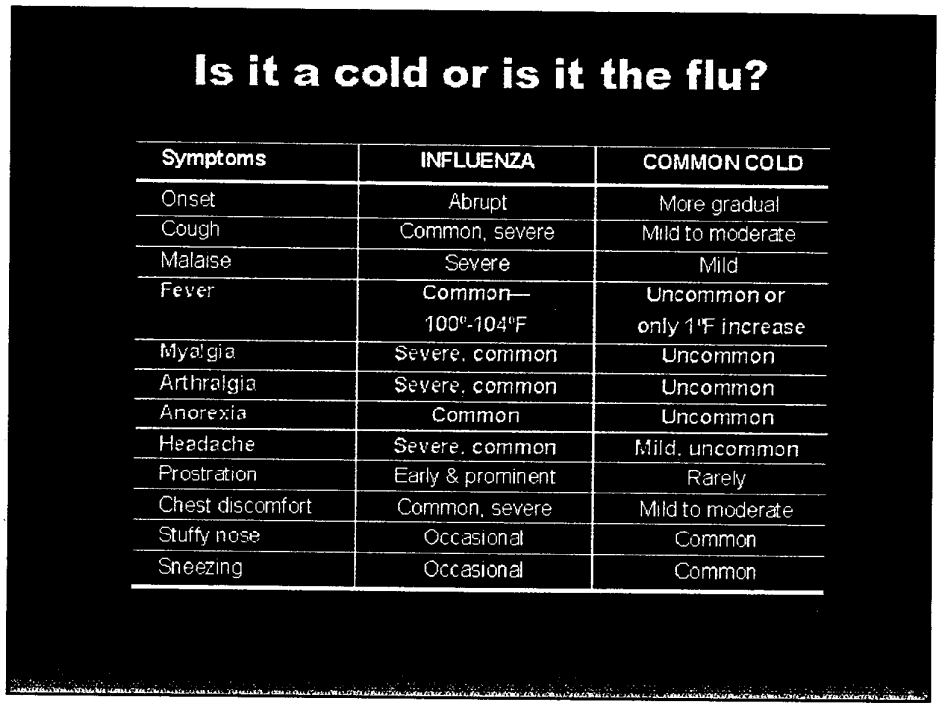
10. Hayden FG, Fritz RS, Lobo MC, et al. Local and systemic cytokine responses during experimental human influenza A virus infection. *J Clin Invest.* 1998;101(3):643-649.



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.

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.



Is it a cold or is it the flu?

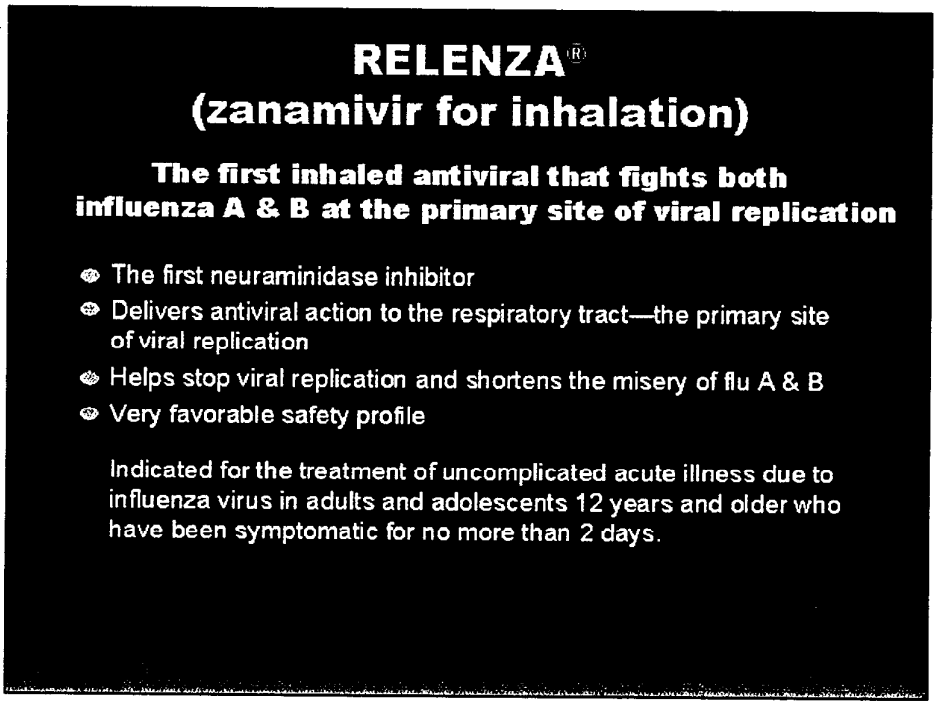
Early flu symptoms can be mistaken for a common cold, but there are significant differences [4,11]:

–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.

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.



RELENZA® (zanamivir for inhalation)—The first inhaled antiviral that fights both influenza A & B at the primary site of viral replication

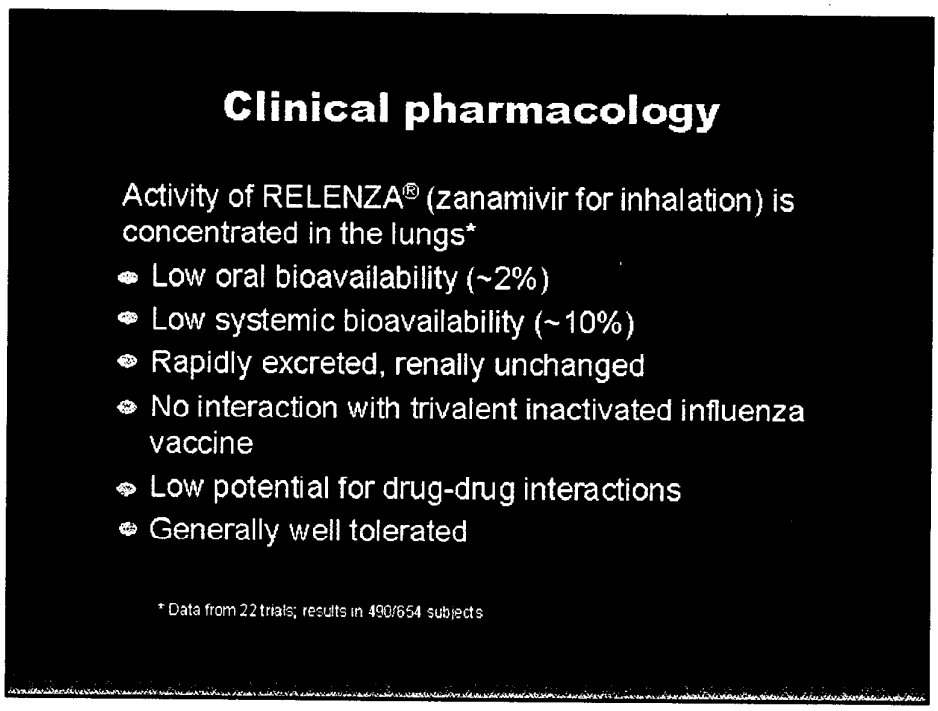
RELENZA offers a logical approach to combatting influenza infection:

–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.



Clinical pharmacology[12]

Activity of RELENZA® (zanamivir for inhalation) 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.

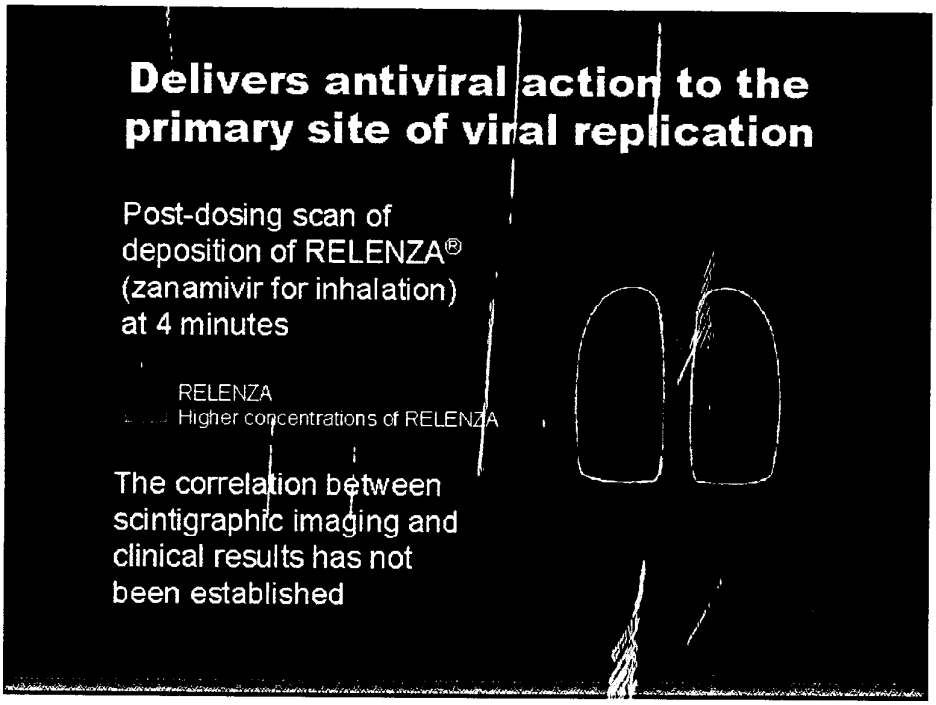
–Low potential for drug-drug interactions.

–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.

12. Data on file, Glaxo Wellcome, Inc., Research Triangle Park, NC.



Delivers antiviral action to the primary site of viral replication

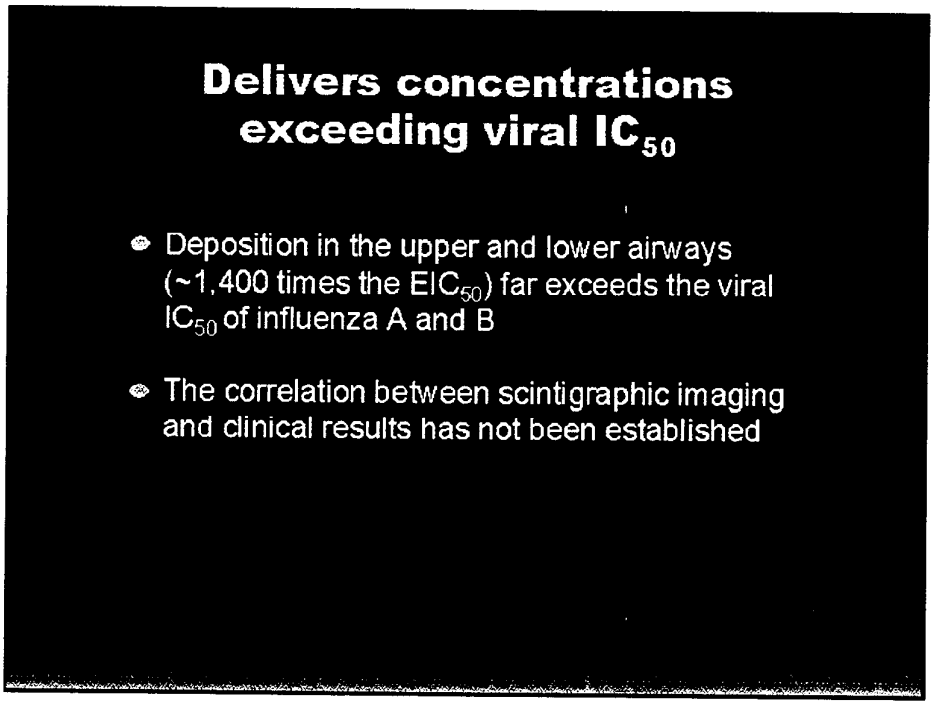
After inhalation of a single technetium-radiolabeled 10-mg dose of RELENZA® (zanamivir for inhalation) by 12 healthy adult volunteers, two-dimensional scintigraphic imaging scans of the lungs showed that[13]:

–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.

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.



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

Deposition of RELENZA® (zanamivir for inhalation) 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.

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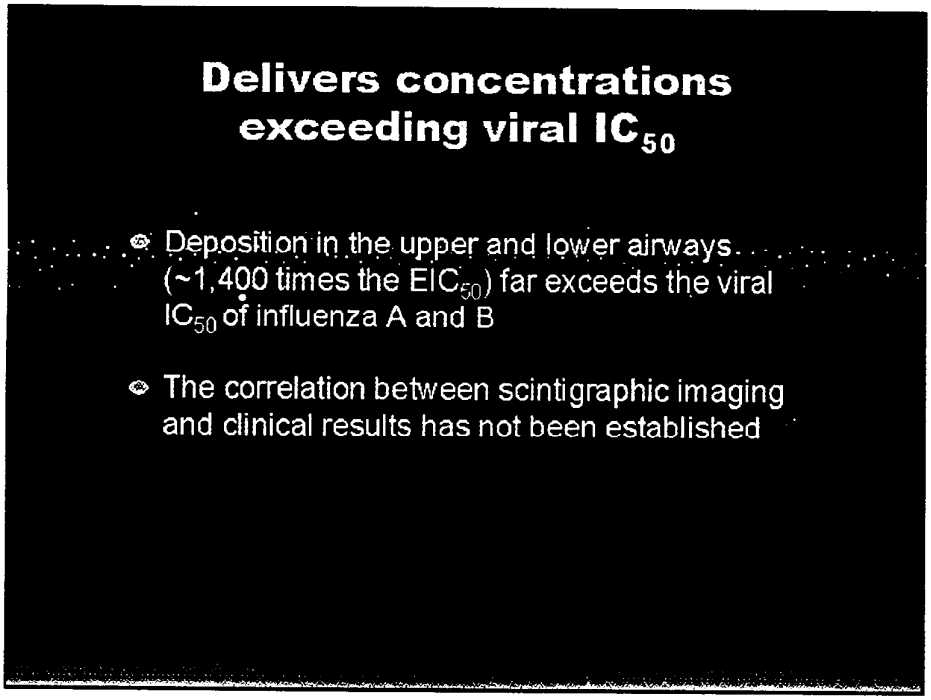

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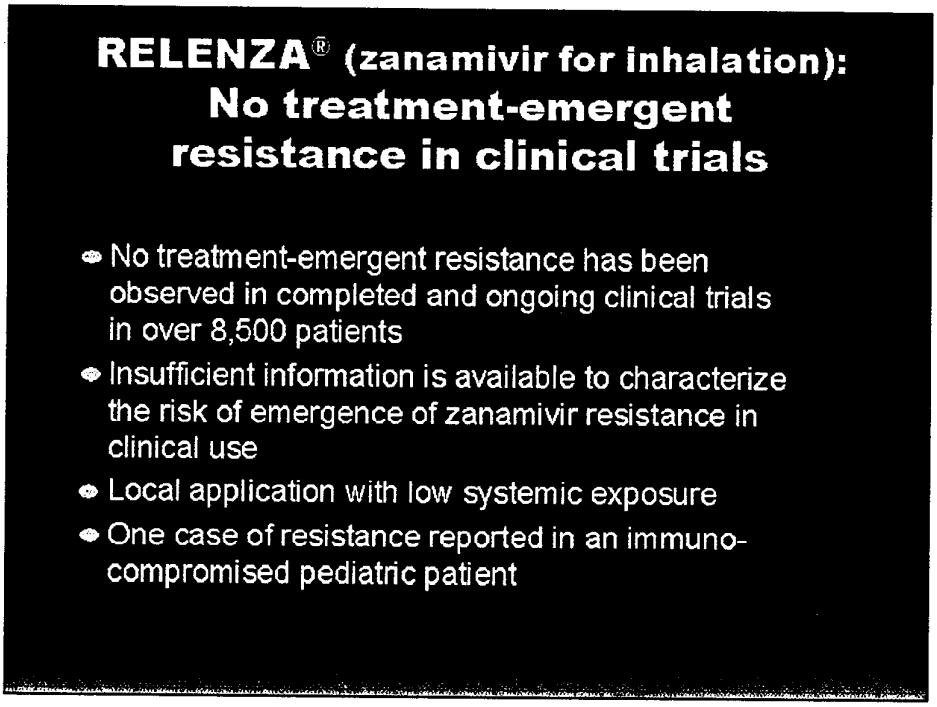


RELENZA® (zanamivir for inhalation):
No treatment-emergent resistance in clinical trials

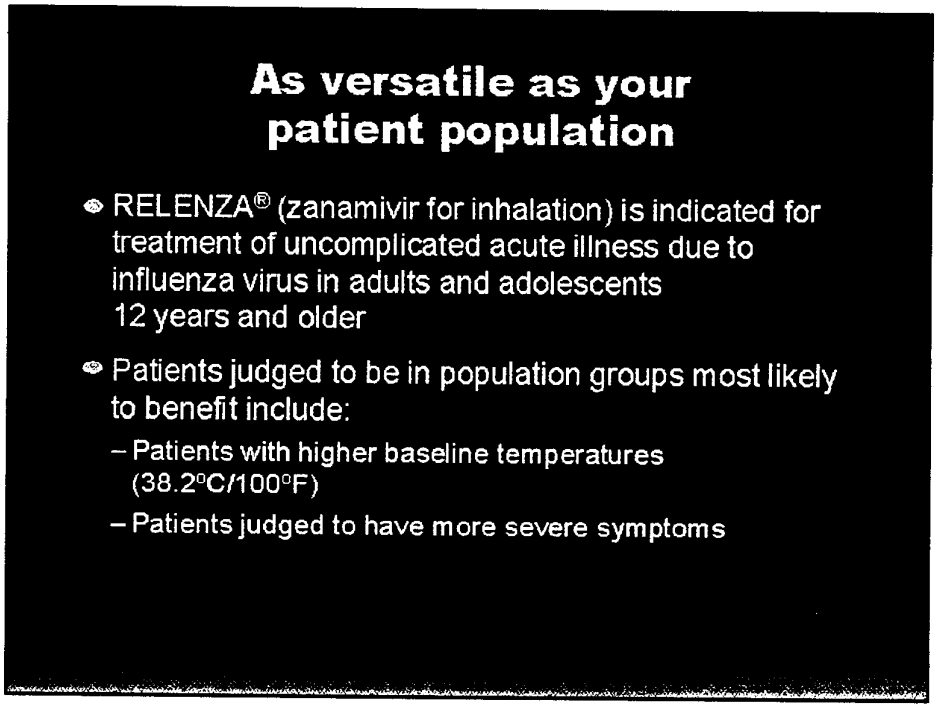
No treatment-emergent resistance has been observed in completed and ongoing clinical trials in over 8,500 patients.[12]

–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.

12. Data on file, Glaxo Wellcome, Inc., Research Triangle Park, NC.



As versatile as your patient population

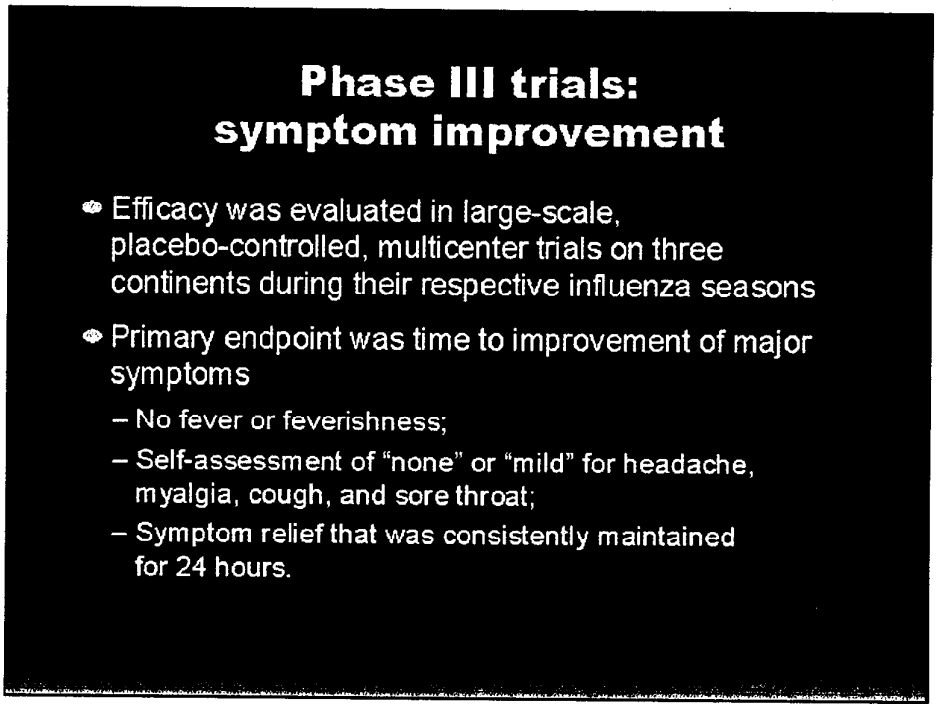
RELENZA® (zanamivir for inhalation) is indicated for the treatment of uncomplicated acute illness due to influenza virus in adults and adolescents 12 years and older.

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.



Phase III trials: symptom improvement

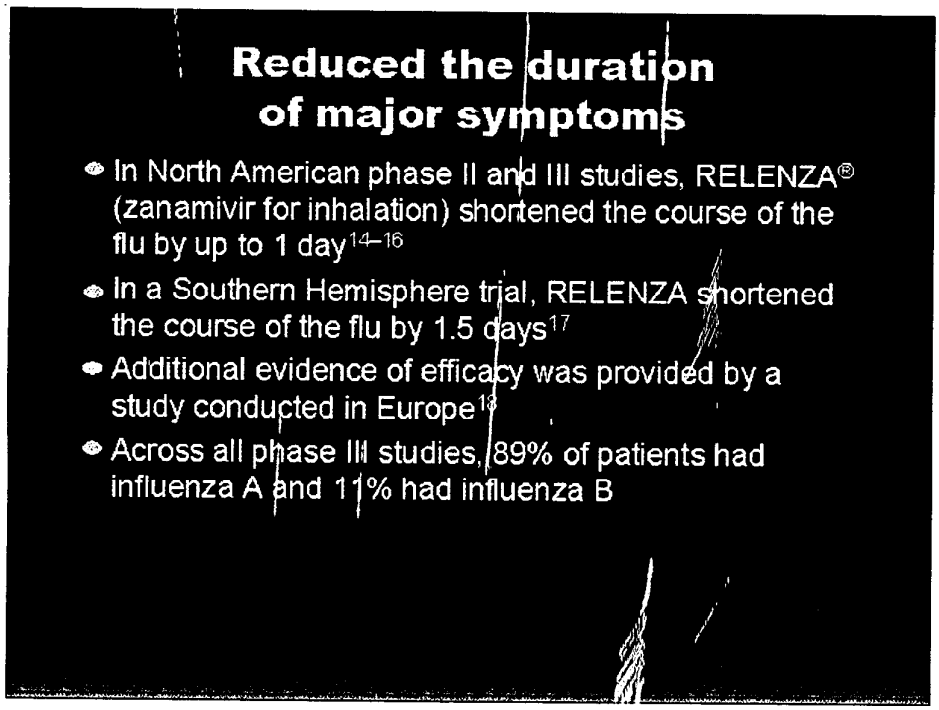
RELENZA® (zanamivir for inhalation) 10 mg inhaled twice daily was studied in placebo-controlled trials in North America, the Southern Hemisphere, and Europe during their respective flu seasons.

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.



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.

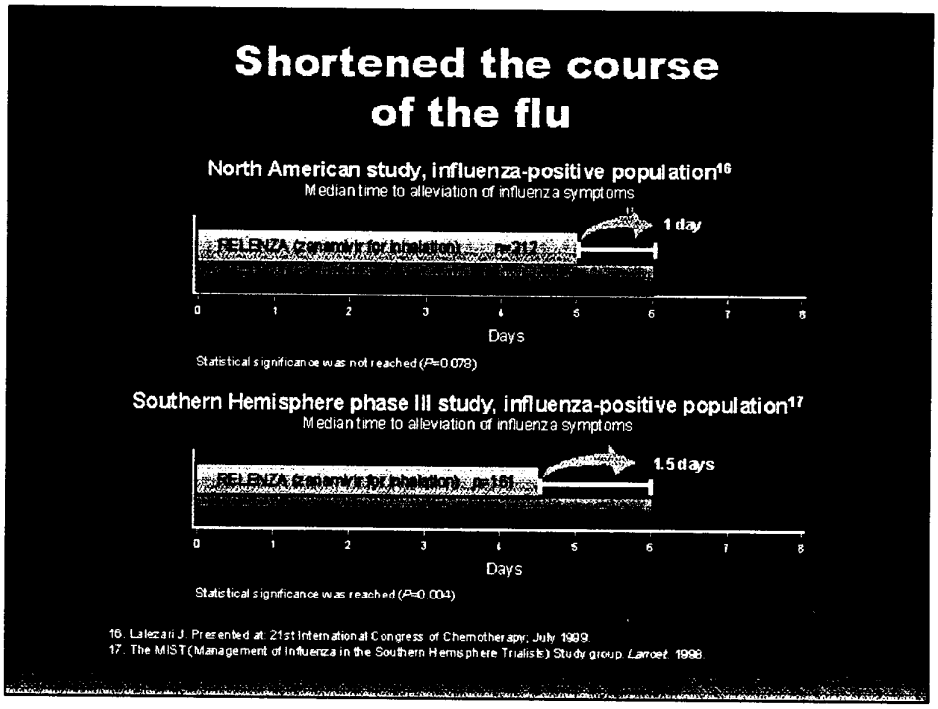
RELENZA® (zanamivir for inhalation) reduced the duration of illness in adults and adolescents 12 years of age and older:

–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]

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, Mancy. Efficacy and safety of the neuraminidase inhibitor zanamivir in the treatment of influenza Ã 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.



RELENZA® (zanamivir for inhalation) 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.[16,17]

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

–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.

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.

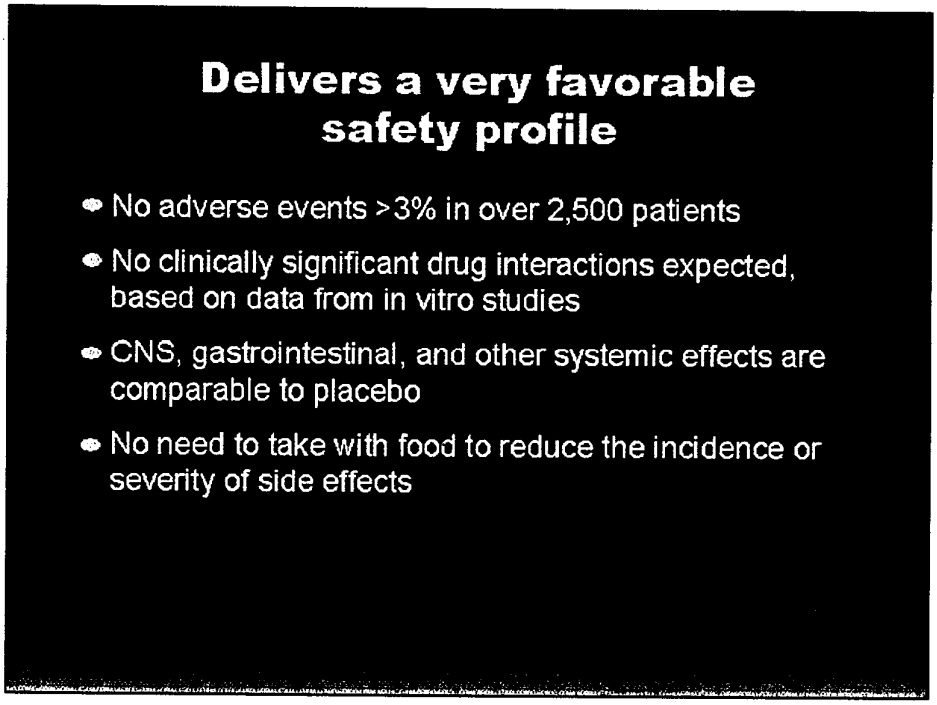
Side effects comparable to placebo with no adverse events >3% in over 2,500 patients

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® (zanamivir for inhalation) 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.



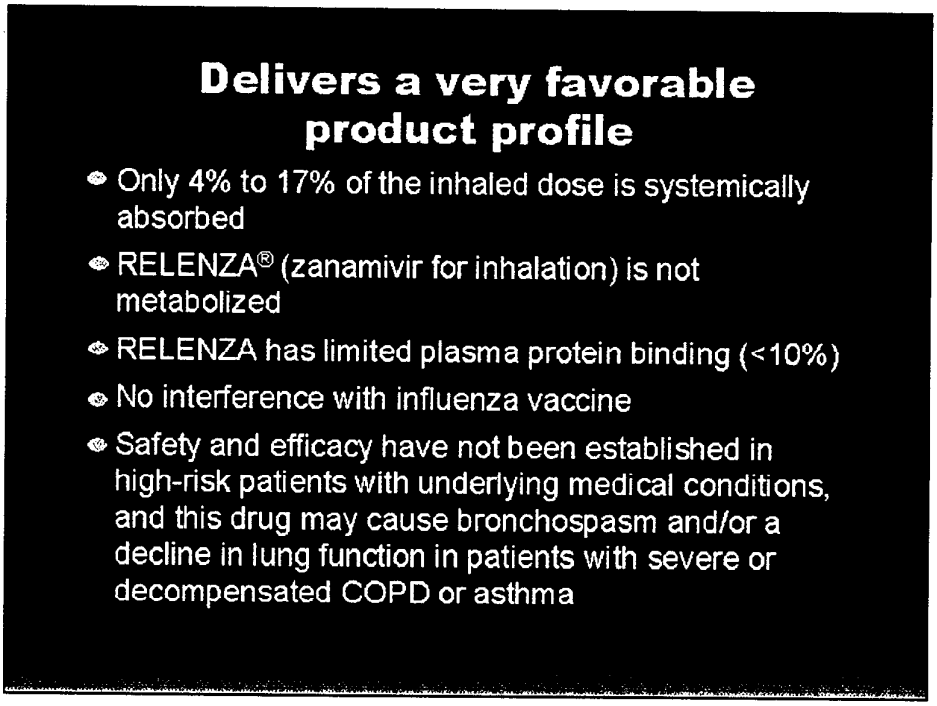
RELENZA® (zanamivir for inhalation) delivers a very favorable safety profile

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.



RELENZA® (zanamivir for inhalation) delivers a very favorable product profile

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

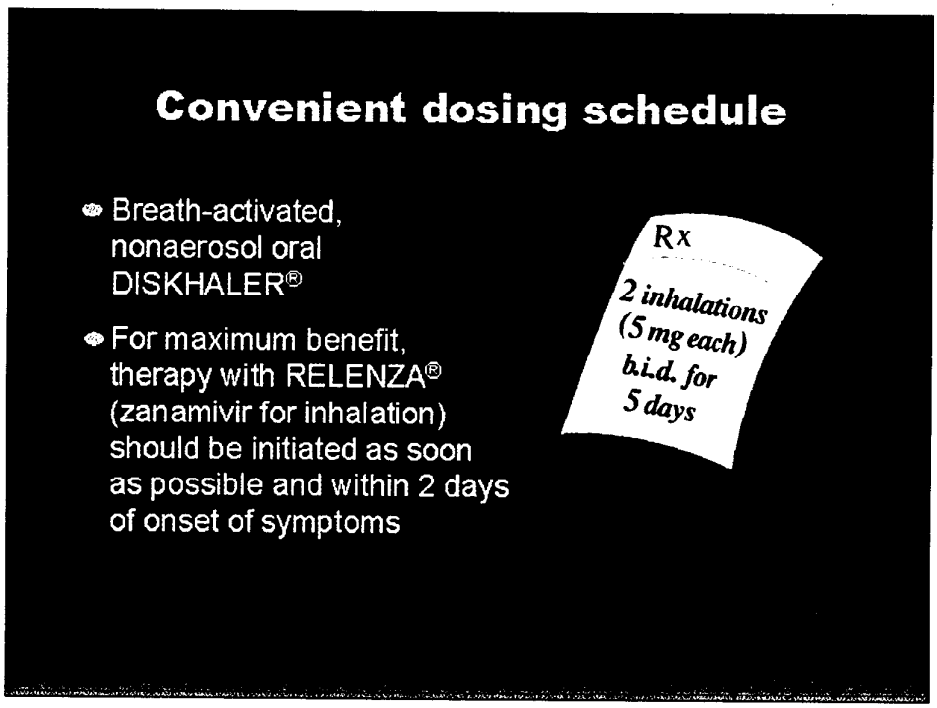
–RELENZA is not metabolized.

–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.



RELENZA® (zanamivir for inhalation) 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.

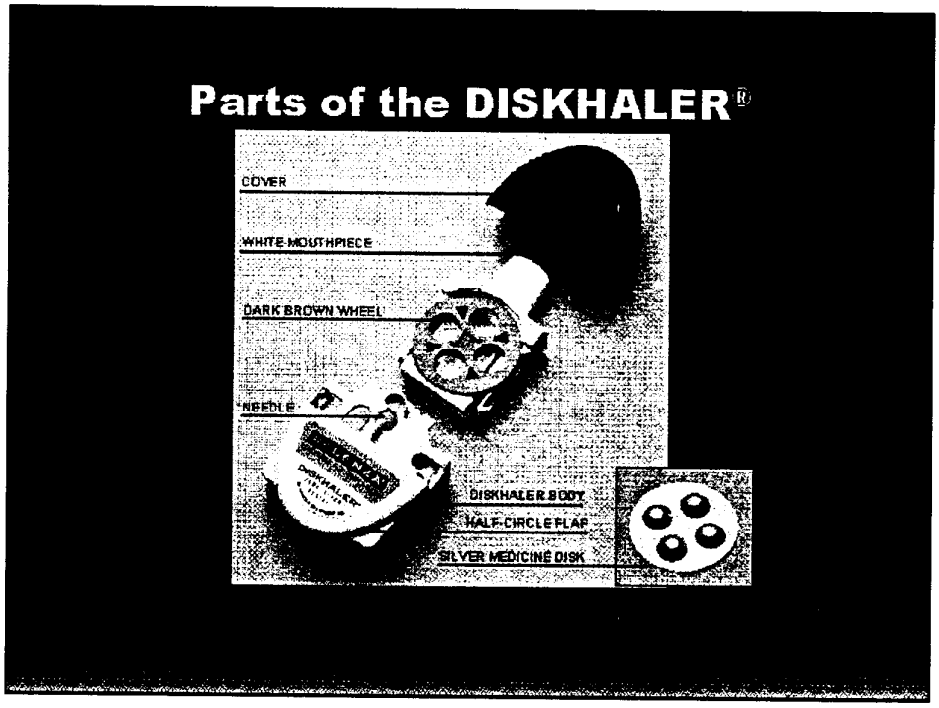
For maximum benefit, therapy with RELENZA should be initiated as soon as possible and within 2 days of onset of symptoms.

DISKHALER® delivery system

RELENZA® (zanamivir for inhalation) 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.



Loading the medicine into the DISKHALER®

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

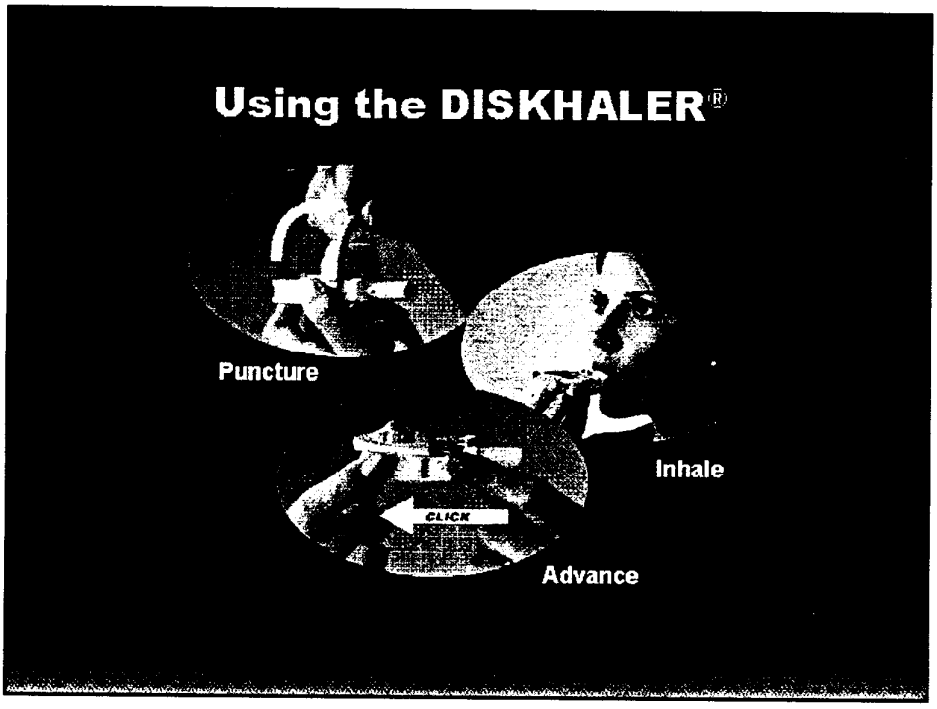
–Remove the blue cover and check inside the mouthpiece to ensure that it's free of foreign objects.

–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.



Puncture, Inhale, and Advance

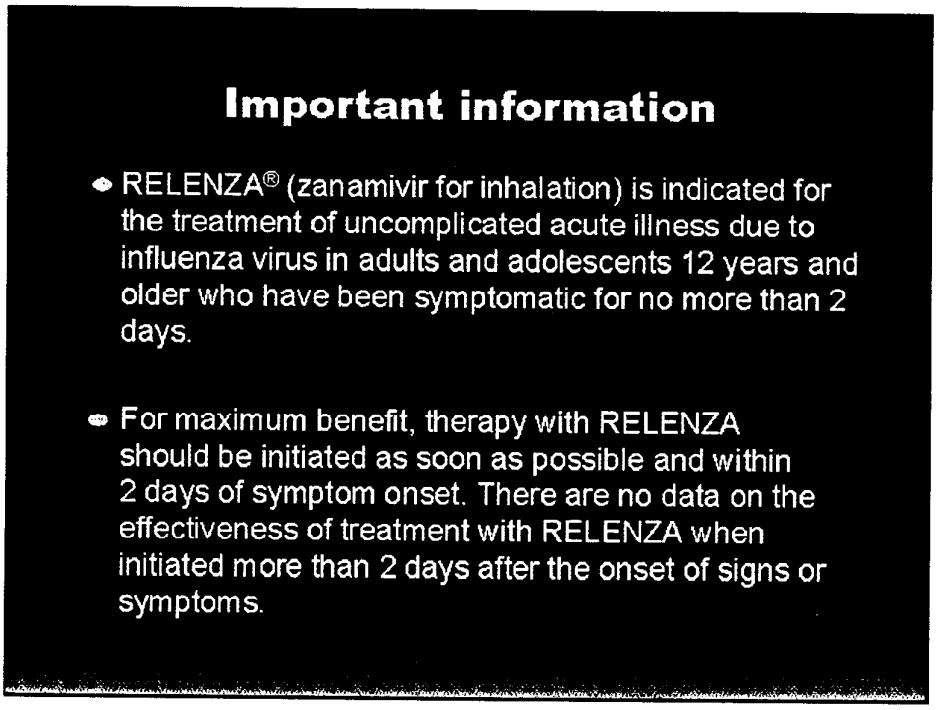
The DISKHALER® only punctures one blister at time, so patients can inhale the correct amount. To take the medication, the patient should:

–Keep the DISKHALER level, lift the flap all the way up to puncture the blister, then click it back down. It's 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.

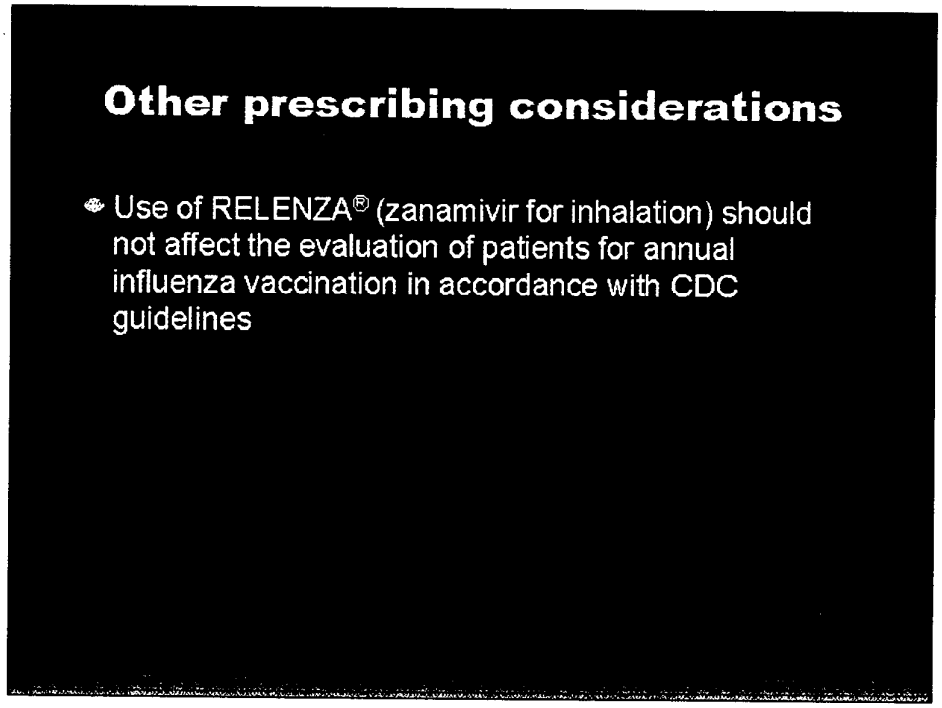
To take the next inhalation, simply repeat the puncture and inhale steps.



Important information

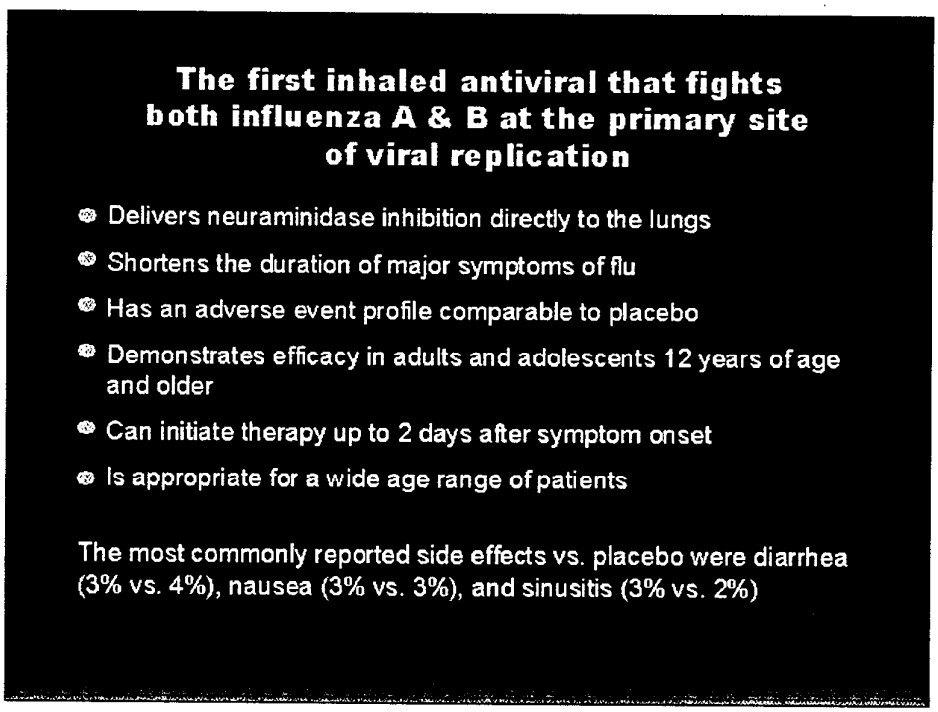
RELENZA® (zanamivir for inhalation) is indicated for the treatment of uncomplicated acute illness due to influenza virus in adults and adolescents 12 years and older who have been symptomatic for no more than 2 days.

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.



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.



RELENZA® (zanamivir for inhalation) is 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.

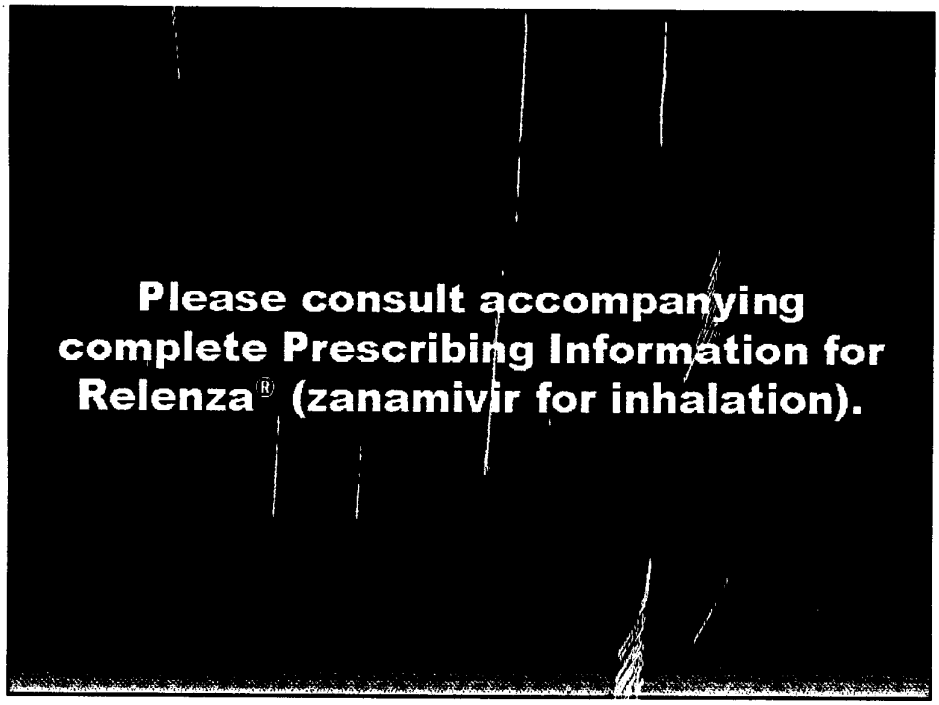
–RELENZA has a very favorable safety profile with adverse events comparable to placebo.

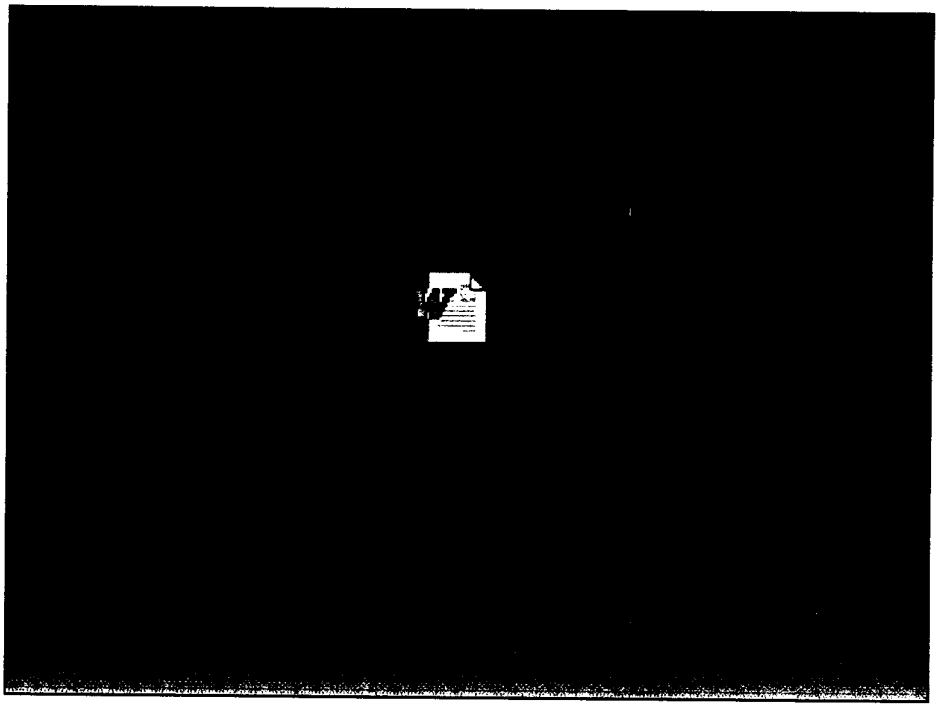
–Efficacy was demonstrated in adults and adolescents 12 years of age and older.

–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%).


Please consult accompanying complete Prescribing Information for Relenza® (zanamivir for inhalation).



WELCOME INSTRUCTIONS

Program Overview

Thank you for participating in the V.I.P. (Valuable Insights from Patients) Trial-Use Program. This program enables you to give your patients an opportunity to try a new therapy for influenza A and B.

Influenza afflicts 25 to 55 million people annually in the United States, resulting in 20,000 deaths and 50,000 to 300,000 hospitalizations.[1,2]

RELENZA® (zanamivir for inhalation) reduces the duration of influenza symptoms when given within 48 hours of symptom onset. RELENZA is the first neuraminidase inhibitor approved by the FDA for the treatment of influenza. 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.

Patient Benefits

Your patients will receive a new therapy for influenza A and B. They will receive a 1-day sample of RELENZA, a 30-minute phone card, which will be activated by completing the Patient Survey, and a care package. By responding to the Patient Survey, your patients will have the opportunity to provide rapid feedback on their experience with RELENZA.

Clinician Benefits

You will receive regularly faxed updates of survey results from your patients, based on their answers to survey questions. This feedback can help you evaluate your patients' experience. If you contract influenza, the National Clinician Influenza Kit allows you to participate as a patient in the V.I.P. Program. You receive a 30-minute phone card, which can be activated by completing the National Clinician Influenza Survey, and a care package.

Enrollment

The V.I.P. Trial-Use Program contains the patient forms, instructions, and samples of RELENZA necessary to enroll 10 of your patients who developed influenza symptoms in the last 48 hours.

If you have any questions about the V.I.P. Trial-Use Program, please call our dedicated Help Desk at 1-888-609-9650 or contact your Glaxo Wellcome representative. Any questions you may have regarding RELENZA should be directed to Glaxo Wellcome at 1-888-825-5249.

For an up-to-date influenza forecast in your area, log on to www.flutrack.com.

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;331:778-784.

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.

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

Please see complete Prescribing Information enclosed in this kit.

GlaxoWellcome

Dear Healthcare Professional:

Glaxo Wellcome Inc. is pleased to announce the availability of RELENZA® (zanamivir for inhalation)—the first antiviral that fights both influenza A and B. 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.

RELENZA, the first neuraminidase inhibitor, is inhaled into the respiratory tract to help stop viral replication and shorten the course of flu-related symptoms. In five well-controlled phase II and III studies, RELENZA reduced the duration of clinically significant symptoms of influenza by up to 1 day in North American trials and by 1.5 days in a Southern Hemisphere study when used within 2 days of symptom onset.

RELENZA is well tolerated with a very favorable safety profile. Side effects were comparable to placebo with no adverse events occurring at an incidence of greater than 3% in over 3,500 patients. RELENZA has low systemic exposure and no known metabolites. Dosage adjustments are not necessary in the elderly, or in patients with hepatic or renal impairment. Additionally, RELENZA does not impair the antibody response to the influenza vaccine.[1]

The following information on inhaled RELENZA is presented for your review:

- Need for RELENZA
- Efficacy
- Safety profile
- Cost and value of RELENZA

Need for RELENZA

A significant issue facing healthcare providers today is the indiscriminate use of antibiotics to treat viral infections. Overuse of antibiotics leads to bacterial resistance and, ultimately, the rising cost of treating infectious diseases.[2,3]

RELENZA can be an important addition to your formulary because it treats influenza and meets an essential need for patients and physicians. Influenza is a serious disease, affecting an estimated 108 million Americans and resulting in 20,000 to 40,000 deaths in a given year.[4,5,6] In addition to the morbidity and mortality, the economic burden of this widespread disease is staggering.

Each year, influenza and its complications can result in:

- Approximately 314,000 hospitalizations[4]
  - $1,012.4 million to treat Medicare patients with influenza A[7]
  - $749.5 million to treat Medicare patients with influenza B[7]
- Up to 24 million medical care visits[4]
- Total direct and indirect costs that can exceed $12 billion[5]
- Loss of productivity
  - 315 million restricted-activity days (1994)[6]
  - average of 3 workdays lost per influenza episode[8]

More specifically, a recent breakdown of the cost of influenza found that the average total cost per hospitalized patient was $3,251.04 and the average cost for emergency room treatment was $141.89.[9]

Until now, the only approaches to managing influenza included vaccination and antiviral agents indicated solely for the treatment and prophylaxis of influenza A. Vaccination remains the best defense against influenza; however, vaccination works best in healthy adults when the vaccine and the infecting strain are closely matched.[5,10] Poor immune response among the elderly and low rates of vaccination reduce the efficacy of vaccines.[5,10,11]

The available antiviral agents, amantadine and rimantadine, are not effective against influenza B.[12] This is a serious drawback because influenza B is responsible for approximately 20% of influenza epidemics, and is sometimes the predominant strain in a given year.[12] Moreover, these agents can engender viral resistance.[13,14] RELENZA is indicated for the treatment of both influenza A and B. No treatment-emergent resistance in uncomplicated influenza has been seen in clinical trials. Insufficient information is available to characterize the risk of the emergence of zanamivir resistance in clinical use.

Safety Profile

A total of 3,809 patients participating in clinical trials were included in the safety evaluation. Sixty percent of these patients received RELENZA, and 40% received placebo. No adverse event occurred with an incidence greater than 3% in the group receiving RELENZA. The most common adverse events are summarized in Table 1.

Table 1. Summary of Adverse Events Occurring During Treatment with an Incidence ≥ 1.5%

Adverse Event	RELENZA		
	10 mg Twice-Daily Inhaled (n=1132)	All Dosing Regimens* (n=2289)	Placebo† (n=1520)
Headache	2%	2%	3%
Diarrhea	3%	3%	4%
Nausea	3%	3%	3%
Vomiting	1%	1%	2%
Nasal signs and symptoms	2%	3%	3%
Bronchitis	2%	2%	3%
Cough	2%	2%	3%
Sinusitis	3%	2%	2%
Ear, nose, or throat infection	2%	1%	2%
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.

Laboratory abnormalities including elevation of liver enzymes and creatinine phosphokinase, lymphopenia, and neutropenia were reported in similar proportions among patients receiving RELENZA and those receiving placebo.

No differences in tolerability were observed between patients ≥65 years of age and younger patients. In addition, no differences in tolerability were observed between patients 12 to 16 years of age and young adults. Based on data from in vitro studies, no clinically significant pharmacokinetic drug interactions are predicted.

The safety and tolerability of RELENZA have not been established in pregnant or lactating women. While there have been no reports of overdose, orally inhaled doses up to 64 mg/day produced adverse effects similar to those seen at the recommended dose.

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. No information is available concerning the use of RELENZA in patients ill enough to be considered for imminent hospitalization. No data are available on the effectiveness of RELENZA when treatment is initiated more than 2 days after the onset of signs or symptoms.

A study of 138 patients confirmed that RELENZA did not impair the protective immune response to influenza vaccine.[1] RELENZA should not affect the evaluation of patients for annual influenza vaccination in accordance with CDC guidelines.

Efficacy

Five placebo-controlled, double-blind, randomized, multicenter, prospective, phase II and III studies were done to evaluate the efficacy of RELENZA in the treatment of acute influenza A and B. Across all phase III studies, 89% of patients had influenza A and 11% had influenza B. Patients at least 12 years of age were required to present within 2 days of influenza onset. They were also required to have fever or feverishness and at least two other designated flu-like symptoms. A total of 1,133 patients received RELENZA (10 mg inhaled twice daily for 5 days); 1,102 patients received placebo.

The primary efficacy endpoint was time to alleviation of clinically significant influenza symptoms. The specific symptoms evaluated varied slightly between studies, but included absence of fever (temperature <37.8°C and/or absence of feverishness), and a self-assessment of "mild" or "none" for headache, myalgia, cough, and sore throat. Symptom alleviation was required to be maintained for 24 hours.

In two phase II studies, RELENZA, when given within 2 days of symptom onset, reduced the time to symptom alleviation by 1 to 1.5 days compared with placebo (Table 2). RELENZA reduced the duration of major symptoms of influenza and was shown to be effective in the treatment of influenza A and B in adolescents and adults.

Table 2. Median Time to Alleviation of Symptoms[15,16]

Influenza-Positive Patient Population	Median Time to Symptom Alleviation		*P*–value
	RELENZA	Placebo	
MIST-Southern Hemisphere Study	4.5 days (n=161)	6.0 days (n=160)	0.004
North American Study	5.0 days (n=312)	6.0 days (n=257)	0.078

Cost

Strength	Package Size	NDC Number	Net Wholesale Price (NWP)‡
RELENZA® 5 mg per blister	Four double-foil blisters (two doses)	0173-0681-01	$37.00

‡NWP= List price to wholesalers and warehousing chains, not including prompt pay, stocking or distribution allowances, or other discounts, rebates, or chargebacks. It may not represent prices charged to other customers.

The Value of RELENZA

Inhaled RELENZA offers physicians an important option in influenza management—– an effective antiviral that is indicated for the treatment of both influenza A and B and has a favorable safety profile. RELENZA is an inhaled viral neuraminidase inhibitor that reduces the duration of major influenza symptoms in adults and adolescents 12 years of age and older. RELENZA is well tolerated, with an incidence of adverse events comparable to placebo. In over 3,500 patients no adverse events occurred with an incidence greater than 3%.

Therapy with RELENZA should be administered within 2 days after symptom onset. Patients should be shown how to use the DISKHALER®, including a demonstration whenever possible. For more information on using the RELENZA DISKHALER, please view the attached CD-ROM monograph.

Glaxo Wellcome Inc., a leader in antiviral research and care, is committed to fighting disease by bringing innovative medicines and services to patients and the healthcare providers who serve them. We hope this letter provides the information you need to review RELENZA for your formulary. If we can provide further information please contact the Glaxo Wellcome Medical Information Department at **1-888-TALK2GW (1-888-825-5249)**.

Sincerely,

Glaxo Wellcome Inc.

Enclosures

Please consult the enclosed complete Prescribing Information for RELENZA.

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

References

1. Webster A, Boyce M, Edmundson S, et al. Coadministration of orally inhaled zanamivir with inactivated trivalent influenza vaccine does not adversely affect the production of antihaemagglutinin antibodies in the serum of healthy volunteers. *Clin Pharmacokinet.* 1999;36(suppl 1):51-58.
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15. The MIST (*Management of Influenza in the Southern Hemisphere Trialists*) Study group. Randomised trial of influenza A and B virus infections. *Lancet.* December 12, 1998;352:1877-1881.
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.